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EXPERT PANEL MEETING
March 11-12, 2021

Cosmetic Ingredient Review

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MEMORANDUM

To: The Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 157th Meeting of the Expert Panel — Thursday and Friday, March 11-12, 2021
Date: February 16, 2021

Welcome to the first Panel Meeting of 2021! The agenda and accompanying materials for the 157th Expert Panel Meeting to be held on March 11-12, 2021 are now available. The location is the ***same*** – this meeting will be held virtually! Invitations (3 of them) to join the meeting will arrive separately in your email inbox. Panel members and liaisons will be registered ***automatically***. However, other interested parties may register to attend in advance of the meeting at the meeting page:

https://www.cir-safety.org/meeting/157th-expert-panel-meeting

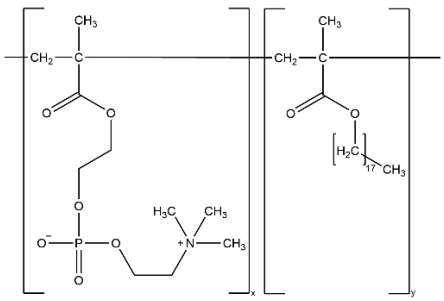
The meeting agenda includes the consideration of 15 reports advancing in the review process, including 7 final reports, 6 tentative reports, and 2 draft reports. Also on the agenda, are 2 administrative items: the Draft 2022 Priorities and a new iteration of the Hair Dye Epidemiology document.

As is usual at the beginning of a new year, we requested and received updated Frequency of Use (FOU) information from the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP). We noticed a general decrease in FOU across many ingredients in this update. Our understanding is that this overall decrease is the result of a deliberate "cleaning up," wherein old reports of use, which could not be validated as current, have now been deleted.

Team Meetings

Draft Reports - there are 2 draft reports for review – Sufficient data to proceed or issue an IDA?

1. Phosphorylcholine Polymers – DR (Wilbur) – This is the first time the Expert Panel for Cosmetic Ingredient Safety (Panel) is reviewing the safety of these 8 acryloyloxyethyl phosphorylcholine polymers. It should be noted that a Scientific Literature Review (SLR) Notice to Proceed (NTP) was announced on May 19, 2020. This announcement was made because an intensive search of the published information on Acryloyloxyethyl Phosphorylcholine Polymers resulted in insufficient information to justify preparation of a formal SLR. Use concentration data and in vitro skin and ocular irritation data were received from the Council. These data are enclosed and summarized in the draft report, along with the limited safety test data that have been identified in the published literature. Additionally, data (toxicity and other relevant data) on poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate), which is remarkably similar structurally to Polyquaternium-51 (which is poly(2-methacryloyloxyethyl phosphorylcholine-co-n-***propyl*** methacrylate)) are included in this safety assessment. The Panel will need to determine the relevance of these data.



   According to 2021 VCRP data, Polyquaternium-51 is reported to be used in 275 cosmetic products (245 leave-on products and 30 rinse-off products). Of the acryloyloxyethyl phosphorylcholine polymers that are being reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey completed in 2019 - 2020 and provided by the Council in 2020 indicate that Polyquaternium-51 is being used at maximum use concentrations up to 0.14% in leave-on products (face and neck products (not spray)). This is the highest maximum cosmetic use concentration reported for the acryloyloxyethyl phosphorylcholine polymers. Polyquaternium-61 is used at the highest concentration in rinse-off products, at maximum use concentrations up to 0.01% in (hair conditioners).

   After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a tentative report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

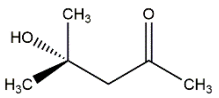
2. Sage – DR (Preethi) – This is the first time the Panel is reviewing the safety of these 12 *Salvia officinalis*-derived ingredients. An SLR was announced on November 23, 2020. Comments, use concentration data, specifications, and summary information were received from the Council; and, the draft report has been revised to address these comments and information.

   According to 2021 VCRP survey data, Salvia Officinalis (Sage) Leaf Extract is reported to have the greatest frequency of use; it is reported to be used in 213 formulations, 116 of which are rinse-off formulations. The other ingredients have 87 or fewer reported uses. The results of the concentration of use survey conducted by the Council in 2020 indicate Salvia Officinalis (Sage) Leaf Extract also has the highest reported concentration of use; it is used at up to 0.38% in other skin care preparations. A few of the *Salvia officinalis* (sage)-derived ingredients are reported to be used in products applied near the eye, such as Salvia Officinalis (Sage) Leaf at up to 0.0001% in eye lotions, and in products that can result in incidental ingestion (e.g., Salvia Officinalis (Sage) Oil at up to 0.011% in dentifrices). Additionally, some of the ingredients are used in formulations that could come in contact with mucous membranes, such as Salvia Officinalis (Sage) Oil at up to 0.02% in bath soaps and detergent. Furthermore, some of the *Salvia officinalis* (sage)-derived ingredients are used in cosmetic spray formulations, and could possibly be inhaled. For example, Salvia Officinalis (Sage) Leaf Extract is reported to be used in pump and aerosol hair sprays at up to 0.0001% and 0.002%, respectively, Salvia Officinalis (Sage) Extract is reported to be used in underarm deodorant spray at up to 0.0011%, and Salvia Officinalis (Sage) Leaf Oil is reported to be used in pump spray suntan formulations at up to 0.012%.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a tentative report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

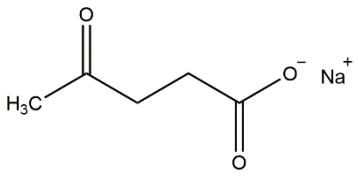
Draft Tentative Reports – there are 6 draft tentative reports for consideration.

1. Diacetone Alcohol – TR (Priya) – At the September 2020 meeting, the Panel issued an IDA for this ingredient. In order to come to a conclusion of safety, the Panel requested impurities data. Since the issuance of the IDA, CIR has not received any new data.



   The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a tentative report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

2. Levulinic Acid and Sodium Levulinate – TR (Preethi) – At the September 2020 meeting, the Panel issued an IDA, and the following data were requested. No data have been received.



   - Impurities
   - 28-day dermal toxicity data; if absorbed, other endpoints (e.g., developmental and reproductive toxicity data), may be needed
   - Ocular irritation data at, or above, the highest reported leave-on concentration, 0.57%

   Based on the proceedings and comments from the September 2020 meeting, a draft Discussion has been prepared; however, additional discussion points are requested. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a tentative report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

3. Tea Tree – TR (Monice) – At the December 2020 meeting, the Panel noted the report was robust with data for a substance with the generic name tea tree oil, and the Panel considered these data relevant to the 2 oil ingredients in the report (i.e., Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Oil and Melaleuca Alternifolia (Tea Tree) Leaf Oil).

   However, it was not clear to the Panel whether those data are also relevant to the 6 non-oil ingredients (i.e. Melaleuca Alternifolia (Tea Tree) Extract, Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract, Melaleuca Alternifolia (Tea Tree) Leaf, Melaleuca Alternifolia (Tea Tree) Leaf Extract, Melaleuca Alternifolia (Tea Tree) Leaf Powder, and Melaleuca Alternifolia (Tea Tree) Leaf Water). Accordingly, an IDA was issued requesting the following:

   - methods of manufacture, composition, and impurity data for the non-oil ingredients (named above); if these are significantly different than that of the oils, then the following are also needed:
     - irritation and sensitization data for Melaleuca Alternifolia (Tea Tree) Extract at the expected maximum concentration of use, and
     - other toxicity endpoints, specifically to include genotoxicity data

   VCRP data for 2021 have been received, and the frequency of use data have been updated accordingly. Frequency of use decreased for most of the ingredients, and Melaleuca Alternifolia (Tea Tree) Leaf Powder, which was reported to be used in 3 formulations in 2020, is now, not reported to be used. Most notably, the frequency of use for Melaleuca Alternifolia (Tea Tree) Leaf Oil decreased from 724 reported used in 2020 to 536 reported uses in 2021, with uses reported in leave-on formulations decreasing from 418 to 300, and in formulations with dermal contact decreasing from 557 to 409.

The following unpublished data on Melaleuca Alternifolia (Tea Tree) Leaf Extract have recently been submitted by the Council, and are included in the report (as indicated by yellow highlighting):

1. Native Extracts. 2020. Safety Data Sheet: Melaleuca Alternifolia (Tea Tree) Leaf Extract.
2. Southern Cross University. 2020. Certificate of Analysis Fragrance Allergens: Melaleuca Alternifolia (Tea Tree) Leaf Extract.
3. Southern Cross University. 2018. Certificate of Analysis: Melaleuca Alternifolia (Tea Tree) Leaf Extract.
4. Native Extracts. 2020. Manufacturing Concentrate Flowchart.
5. Native Extracts. 2019. Manufacturing Oil Flowchart. [Not included in the report; please indicate if you find the information relevant to the safety of these ingredients.]
6. Southern Cross University. 2020. Certificate of Analysis Fragrance Allergens: Vitis Vinifera (Grape) Seed Oil and Melaleuca Alternifolia (Tea Tree) Leaf Extract.
7. Native Extracts. 2018. Safety Data Sheet: Vitis Vinifera (Grape) Seed Oil and Melaleuca Alternifolia (Tea Tree) Leaf Extract.
8. Southern Cross University. 2018. Certificate of Analysis (fatty acids): Vitis Vinifera (Grape) Seed Oil and Melaleuca Alternifolia (Tea Tree) Leaf Extract.

Data obtained from an industry video describing the manufacture of tea tree oil were also added to the report (and indicated by yellow highlighting). A literature review on tea tree oil was submitted by the Australian Tea Tree Industry Association (ATTIA), as were comments following the December meeting. Please note, while the entire literature review that was received is included for your review, the only new data obtained from it were a 4-h semi-occlusive irritation study in rabbits.

Based on the proceedings and comments from the December 2020 meeting, a draft Discussion has been prepared. The Panel should carefully consider and discuss the data (or lack thereof), and the draft Abstract and draft Discussion presented in this report. A tentative report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion should then be issued.

4. Red Algae – TR (Priya) – At the September 2020 meeting, the Panel issued an IDA for this ingredient group, and the following data were requested:

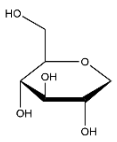
- composition/impurities data for ingredients without a GRAS designation;
- a 28-day dermal toxicity assay of Corallina Officinalis Extract at the current maximum concentration of use (2%); if positive, systemic toxicity data such as DART and genotoxicity may be needed; and
- dermal sensitization data on all ingredients

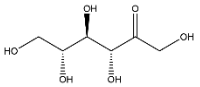
It should be noted that, as suggested by the Council and agreed upon by the Panel at the September meeting, Kappaphycus Alvarezii Extract has been added to this ingredient group, as it is derived from a red algae species. Concentrations of use for this ingredient have been received and incorporated into the report.

Since the review of the Draft Report, the Council has provided considerable additional information regarding the red-algae derived ingredients. These data are summarized in Priya's transmittal memo and have been marked in the report with yellow highlight.

A draft Discussion has been incorporated into the report, based on the proceedings and comments from the September meeting. The Panel should carefully consider and discuss the data (or lack thereof), and the draft Abstract and draft Discussion presented in this report. A tentative report with a safe as used, safe with qualifications, insufficient, or unsafe conclusion should then be issued.

5. Saccharide Humectants – TR (Wilbur) – At the September 2020 meeting, the Panel issued an IDA for these 7 ingredients, with the following data requests:





- method of manufacture, impurities, and composition data on all ingredients/ingredient mixtures
- confirmation of the lack of skin penetration of these ingredients/ingredient mixtures
- composition of glucose and fructose in the ingredient mixtures; if the 2 monosaccharides are present in sufficient amounts, the available negative data on glucose and fructose skin penetration can be used to evaluate the skin penetration potential of saccharide humectant ingredient mixtures
- 28-day dermal toxicity data on Saccharide Isomerate at cosmetic use concentrations up to 2.8%

In response to the IDA, the following data were received from the Council, and have been added to the draft report (and are highlighted in report text):

- chemical properties of Arabinose
- methods of production of Arabinose and Saccharide Isomerate
- composition/Impurities data on Saccharide Isomerate
- dermal penetration statement on Saccharide Isomerate
- acute oral toxicity data on Saccharide Isomerate
- in vitro genotoxicity data on Saccharide Isomerate
- animal and human skin irritation data on Saccharide Isomerate
- animal and human skin sensitization data on Saccharide Isomerate
- Animal and in vitro phototoxicity/photosensitization data on Saccharide Isomerate
- Ocular irritation data on Saccharide Isomerate

Additionally, the report has been revised to include 2021 FDA VCRP data that were received in January of this year. Saccharide Isomerate, the most frequently used saccharide humectant, was used in 494 formulations in 2020 and is being used in 352 formulations in 2021.

Based on the proceedings and comments from the September 2020 meeting, a draft Discussion has been included. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe as used, safe with qualifications, insufficient data, unsafe, or split conclusion.

6. Silicates – TAR (Christina) – At the September 2020 meeting, the Panel issued an IDA for these ingredients. The additional data needed to determine safety were:

- Method of manufacturing, with specific focus on the origin of raw materials (synthetic versus mined derivation)
- Composition and impurities data, specifically percent quantification of any crystalline silica/silicate
- Inhalation toxicity data

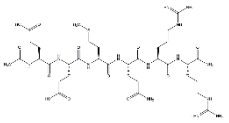
Since the issuance of the IDA, CIR has received unpublished data on composition and impurities for Magnesium Aluminum Silicate and Sodium Magnesium Silicate and crystallinity content for Aluminum Calcium Sodium Silicate and Sodium Silver Aluminum Silicate. These data have been incorporated into the report and are highlighted to aid in the Panel's review. Additionally, inhalation toxicity summary data and the conclusion from the synthetically-derived amorphous silica and hydrated silica report, regulatory standards for OSHA and NIOSH, and findings from the ATSDR report on silica have been incorporated and highlighted.

The CIR Science and Support Committee has provided comments, primarily with regard to the discussion of crystalline silica as a potential contaminant. Correspondence from the Synthetic Amorphous Silica and Silicate Industry Association (SASSI) regarding the Draft Amended Report is also included in this report package. SASSI stated they have no additional data to submit related to the three silicates manufactured by SASSI member companies for use in cosmetics, and reiterated their statement that only Calcium Silicate, Sodium Metasilicate, and Sodium Silicate are marketed to the cosmetics industry by SASSI members. Additionally, CIR has received 2021 VCRP data and the Use Table has been updated. Uses have decreased for most ingredients.

Based on the proceedings and comments from the September 2020 meeting, a draft Discussion has been included. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion.

Draft Final Reports - there are 7 draft final reports for consideration. After reviewing these drafts, especially the rationales provided in the Discussion sections, the Panel should issue these as final reports, as appropriate.

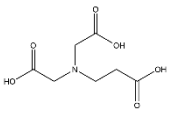
1. Acetyl Hexapeptide-8 Amide – FR (Wilbur) – At the December 2020 meeting, the Panel issued a Revised Tentative Report with a conclusion stating that Acetyl Hexapeptide-8 Amide is safe in cosmetics at concentrations up to 0.005%, and that the available data are insufficient for evaluating safety at higher concentrations. It was agreed that a no-observed-adverse-effect-level (NOAEL) for type I and type III collagen synthesis would be needed to evaluate the safety of Acetyl Hexapeptide-8 Amide in cosmetic products at concentrations > 0.005%. These data have not been provided.



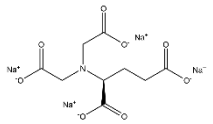
This report has been revised to address comments and to include 2021 FDA VCRP data that were received in January of this year. It should be noted that these data indicate that the reported use frequency of Acetyl Hexapeptide-8 Amide in cosmetics has decreased by more than 100 uses since this safety assessment was reviewed by the Panel in December of last year.

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. After reviewing these documents, the Panel should issue a Final Report with the conclusion that is stated in the first paragraph above.

2. Amino Acid Diacetates – FR (Christina) – At the December 2020 meeting, the Panel issued a Tentative Report with the conclusion that Tetrasodium Glutamate Diacetate is safe in cosmetics in the current practices of use and concentration described in the safety assessment. However, the Panel also concluded that the available data are insufficient to make a determination that Beta-Alanine Diacetic Acid is safe under the intended conditions of use in cosmetic formulations. The additional data needed to determine safety are:



Beta-Alanine Diacetic Acid



Tetrasodium L-Glutamate Diacetate

- Method of manufacturing
- Composition and impurities
- Concentration of use
- Dermal irritation and sensitization data at maximum use concentration
- 28-day dermal toxicity data
    - If positive, developmental and reproductive toxicity and genotoxicity data may be needed

Since the issuance of the Tentative Report, CIR has not received any of the requested data. CIR has received 2021 VCRP data and the Use Table has been updated. Uses for Tetrasodium Glutamate Diacetate have decreased from 977 to 752. The majority of the uses are still in bath soaps and detergents. Use for Beta-Alanine Diacetic Acid decreased from 2 to a single-use in a moisturizing skin care product.

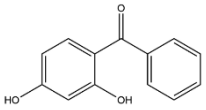
The Panel should review the Abstract, Discussion, and Conclusion, and issue a Final Report.

3. Basic Brown 17 – FR (Christina) – At the December 2020 meeting, the Panel issued a Tentative Report with the conclusion that Basic Brown 17 is safe in the present practices of use and concentration in hair dye products. However, the Panel also concluded that the available data are insufficient to make a determination that Basic Brown 17 is safe under the intended conditions of use in other cosmetic product types. The additional data needed to determine safety were concentration of use and reported function for the non-coloring hair product uses that were reported in the FDA VCRP database, and dermal irritation and sensitization data at maximum use concentration for non-hair coloring products.

   Since the issuance of the Tentative Report, CIR has not received any of the requested data. CIR has received 2021 VCRP data. Total uses for Basic Brown 17 have decreased from 54 to 20, with 17 of these uses reported to be in hair coloring formulations. The number of uses reported in non-coloring hair products remains at 3.

   The Panel should review the Abstract, Discussion, and Conclusion, and issue a Final Report.

4. Benzophenones – FAR (Wilbur) – At the September 2020 meeting of the Panel issued a Tentative Amended Report with the conclusion that Benzophenone-1, -2, -3, -4, -5, -6, -8, -9, -10, -11, and -12 are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The document has been revised to address comments on the Tentative Amended Report that were received from the Council.



   Since the September meeting, a study relating to the tumor promotion potential of Benzophenone-3 was found in the published literature. This study is highlighted in the report text for the Panel's review.

   Summary statements relating to 2021 FDA VCRP data on benzophenones that were received are also highlighted in the report text, and substantial changes in ingredient use frequencies are apparent. For example, the use frequency of Benzophenone-2 (299 uses total), which was the highest use frequency reported in the 1983 report, decreased to a value of 55 in 2021. The use frequency of Benzophenone-4 (240 uses) in the 1983 original report increased substantially to a value of 1226 in 2021. When the 2021 FDA VCRP data are compared with the 2020 data that were reviewed at the September 2020 Panel meeting, decreased use frequencies are apparent. Uses of Benzophenone-2 in 2020 (103 uses) decreased to 55 in 2021, whereas uses of Benzophenone-4 in 2020 (2259 uses) decreased to 1226 in 2021.

   After reviewing these documents, as well as the Abstract, Discussion, and Conclusion of the report, the Panel should be prepared to issue a Final Amended Report

5. Papaya – FR (Priya) – At the December 2020 meeting, the Panel issued a Final Report with the conclusion that the available data are insufficient to make a determination of safety for the 5 *Carica papaya* (papaya)-derived ingredients. In order to come to a conclusion of safety for Carica Papaya (Papaya) Fruit, Carica Papaya (Papaya) Fruit Extract, Carica Papaya (Papaya) Fruit Juice, and Carica Papaya (Papaya) Fruit Water, the Panel requested phototoxicity/photosensitization data. In lieu of these data, the Panel would also accept a clarification on the specific ingredients of the SPF 50 lotion in the existing phototoxicity/photosensitization assays. Genotoxicity data, irritation and sensitization at maximum use concentration, and phototoxicity/photosensitization data are needed to come to a conclusion of safety for Carica Papaya (Papaya) Leaf Extract.

   Since the December 2020 meeting, data regarding a UV profile of a mixture containing 0.006% Carica Papaya (Papaya) Fruit Extract were provided by the Council. There were no spectral peaks in the UVA or UVB for this test substance, and there was not enough information to determine the absorbance wavelength of a peak in the UVC.

   Comments on the Tentative Report were received and addressed. In addition, 2021 FDA VCRP data have been received and incorporated into the report. Compared to 2020 FDA VCRP data, Carica Papaya (Papaya) Fruit Extract, the ingredient with the highest number of uses in this ingredient group, has decreased in the total number of uses (from 349 to 172 formulations).

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

6. Coconut – FR (Christina) – At the September 2020 meeting, the Panel issued a Tentative Report with the conclusion that 7 ingredients, i.e., Cocos Nucifera (Coconut) Fruit, Cocos Nucifera (Coconut) Fruit Extract, Cocos Nucifera (Coconut) Fruit/Fruit Juice Extract, Cocos Nucifera (Coconut) Fruit Juice, Cocos Nucifera (Coconut) Fruit Powder, Cocos Nucifera (Coconut) Fruit Water, and Cocos Nucifera (Coconut) Liquid Endosperm, are safe in cosmetics in the present practices of use and concentration described in this safety assessment. However, the Panel also concluded that the data are insufficient to determine safety of 3 ingredients, i.e., Cocos Nucifera (Coconut) Flower Extract, Cocos Nucifera (Coconut) Flower Nectar Extract, and Cocos Nucifera (Coconut) Shell Powder. The additional data needed to determine the safety of these ingredients as used in cosmetics are:

- Composition and impurities data for Cocos Nucifera (Coconut) Flower Extract, Cocos Nucifera (Coconut) Flower Nectar Extract, and Cocos Nucifera (Coconut) Shell Powder.
- Data on Cocos Nucifera (Coconut) Flower Extract, Cocos Nucifera (Coconut) Flower Nectar Extract, and Cocos Nucifera (Coconut) Shell Powder on the following endpoints:
  - 28-day dermal toxicity, and if positive, DART may be needed
  - Genotoxicity
  - Dermal irritation and sensitization

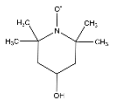
Since September, CIR has received unpublished data on the method of manufacture, composition, and concentration of use for Cocos Nucifera (Coconut) Flower Nectar Extract; these data have been incorporated into the report and are highlighted to aid in the Panel's review. Additionally, comments on the Tentative Report received from the Council have been addressed.

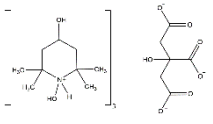
Also, since September, CIR staff have been made aware that Coconut Flower Sugar has been added to the *Dictionary*. This ingredient is defined as the dried, ground nectar obtained from the flowers of *Cocos nucifera*, and it is reported to function as an antioxidant, flavoring agent, skin protectants, skin-conditioning agent-emollient, surfactant-cleansing agent, and pH adjuster. Currently, there are no reported uses for this ingredient in the VCRP, and the Council has reported no concentrations of use. A search of PubMed and the Internet yielded some method of manufacturing and composition data, but no relevant toxicological data for this ingredient. The data for Coconut Flower Sugar have been incorporated into the report and highlighted. **Does the Panel find this ingredient an appropriate addition to this ingredient family?** If so, the Discussion and Conclusion, along with other components of the report, will need to be updated.

The Use Table was updated with 2021 VCRP data. Use for most ingredients has decreased, with the largest occurring in Cocos Nucifera (Coconut) Fruit Extract; total uses decreased from 469 to 327. Uses were reported to have increased in Cocos Nucifera (Coconut) Liquid Endosperm (from 79 to 126).

The Panel should review the Abstract, Discussion, and Conclusion, and issue a Final Report.

7. Hydroxy Tetramethylpiperidine Oxide and Tris(Tetramethylhydroxypiperidinol) Citrate – FR (Preethi) – At the December 2020 meeting the Panel issued a Tentative Report, with the conclusion that these ingredients are safe as used in cosmetics in the present practices of use and concentration.





Corrected concentration of use data for Hydroxy Tetramethylpiperidine Oxide, received from Council in 2020, have been incorporated, reflecting a 0.019% maximum concentration of use in basecoats and undercoats, compared to the previously reported 12.9%. Additionally, 2021 VCRP data have since been received and incorporated in the report, showing an overall decrease in reported uses for Tris(Tetramethylhydroxypiperidinol) Citrate (from 388 to 125 formulations). Of further note, reported uses in sprays have more than halved, and no baby product use has been reported in 2021. These and other changes are highlighted in yellow within the text.

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

Administrative Items - there is 1 draft priorities document, and 1 Hair Dye Epi document.

1. Priorities – The 2022 Draft Priority List is being issued for comment earlier in the process (CIR Procedures require this by June 1st) to allow more time for the acquisition of data. The list is based on stakeholder requests; frequency of use data (FOU) from FDA's VCRP January 21st, 2021; and on CIR staff and Panel workflow. The Grouping/Clustering Working Group should consider groupings therein.

2. Hair Dye Epi – At the December 2018 meeting, the Panel determined to continue monitoring upcoming epidemiological data on the link between personal use of hair dyes and cancer risk, and the conclusion of the document would be re-evaluated based upon the new information on a regular period basis. Since then, 10 new epidemiological studies, including 1 genetic polymorphism study, 4 case-control studies, 2 meta-analysis studies, and 3 prospective cohort studies, have been discovered. The association between hair dye use and risk for various cancer types was investigated, such as breast cancer, leukemia, brain cancer, testicular cancer, non-Hodgkin's lymphoma, follicular lymphoma, and so on. These additional studies are incorporated, highlighted in yellow, for the Panel's consideration.

   The Panel should review this Document, especially noting the data presented in the new studies. If this Document is in agreement with their thinking, it should be finalized and used to replace the version currently posted on the Findings & Resources Documents page (https://www.cir-safety.org/cir-findings). If the Document is not considered to be ready for finalization, specific needs/edits therein should be made evident.

Full Panel Meeting

The Panel will consider the 7 reports to be issued as final safety assessments, followed by the remaining reports advancing in the process (including the tentative reports and draft reports). In addition, a consensus should be reached for the 2 administrative items.

Please remember, the meeting starts at 8:30 am on day 1 and day 2. It is likely that the full Panel session will conclude before lunch on day 2.

Looking forward to seeing you all (virtually)!

Agenda
157th Meeting of the Expert Panel for Cosmetic Ingredient Safety
March 11th - 12th, 2021

Virtual via Microsoft Teams

Thursday, March 11th

8:30 AM	**WELCOME TO THE 157th EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:40 AM	**TEAM MEETINGS**	**Drs. Cohen/Belsito**

Dr. Cohen Team*

FR (PR)	TrisTetramethylhydroxypiperidinol
TR (PR)	Levulinic Acid & Sodium Levulinate
DR (PR)	Sage
FR (PC)	Papaya
TR (PC)	Diacetone Alcohol
TR (PC)	Red Algae
TR (MF)	Tea Tree
Admin (BH)	2022 Draft Priorities
FR (WJ)	Acetyl Hexapeptide-8
FAR (WJ)	Benzophenones
TR (WJ)	Saccharide Humectants
DR (WJ)	Phosphorylcholine Polymers
FR (CB)	Amino Acid Diacetates
FR (CB)	Basic Brown 17
FR (CB)	Coconut
TAR (CB)	Silicates
Admin (JZ)	Hair Dye Epi

Dr. Belsito Team

FR (WJ)	Acetyl Hexapeptide-8
FAR (WJ)	Benzophenones
TR (WJ)	Saccharide Humectants
DR (WJ)	Phosphorylcholine Polymers
FR (CB)	Amino Acid Diacetates
FR (CB)	Basic Brown 17
FR (CB)	Coconut
TAR (CB)	Silicates
Admin (JZ)	Hair Dye Epi
Admin (BH)	2022 Draft Priorities
TR (MF)	Tea Tree
FR (PR)	TrisTetramethylhydroxypiperidinol
TR (PR)	Levulinic Acid & Sodium Levulinate
DR (PR)	Sage
FR (PC)	Papaya
TR (PC)	Diacetone Alcohol
TR (PC)	Red Algae

The purpose of the Cosmetic Ingredient Review and the Expert Panel for Cosmetic Ingredient Safety is to determine those cosmetic ingredients for which there is a reasonable certainty in the judgment of competent scientists that the ingredients are safe under intended conditions of use.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson || (PR): Preethi Raj || (JZ): Jinqiu Zhu

*Team moves to breakout room (for a virtual meeting, this means a separate Microsoft Teams meeting).

Friday, March 12th			
8:30 am		**WELCOME TO THE 157th FULL EXPERT PANEL MEETING**	**Dr. Bergfeld**
8:45 am	Admin	**MINUTES OF THE DECEMBER 2020 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 am		**DIRECTOR'S REPORT**	**Dr. Heldreth**
9:10 am		**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**	

Final Reports

FR (CB)	Amino Acid Diacetates – *Dr. Belsito Reports*
FR (CB)	Coconut – *Dr. Cohen Reports*
FR (CB)	Basic Brown 17 – *Dr. Belsito Reports*
FR (PC)	Papaya – *Dr. Cohen Reports*
FR (PR)	TrisTetramethylhydroxypiperidinol – *Dr. Belsito Reports*
FR (WJ)	Acetyl Hexapeptide-8 – *Dr. Cohen Reports*
FAR (WJ)	Benzophenones – *Dr. Belsito Reports*

Reports Advancing

DR (WJ)	Phosphorylcholine Polymers – *Dr. Cohen Reports*
TR (WJ)	Saccharide Humectants – *Dr. Belsito Reports*
DR (PR)	Sage – *Dr. Cohen Reports*
TR (PR)	Levulinic Acid & Sodium Levulinate – *Dr. Belsito Reports*
TR (PC)	Red Algae – *Dr. Cohen Reports*
TR (PC)	Diacetone Alcohol – *Dr. Belsito Reports*
TAR (CB)	Silicates – *Dr. Cohen Reports*
TR (MF)	Tea Tree – *Dr. Belsito Reports*

Other Items

Admin (JZ)	Hair Dye Epi – *Dr. Cohen Reports*
Admin (BH)	2022 Draft Priorities – *Dr. Belsito Reports*

ADJOURN - *Next meeting Monday and Tuesday,* ***September*** *13-14, 2021, will also be held virtually. Please check the CIR website for details as the meeting approaches.*

On the basis of all data and information submitted, and after following all of the Procedures (https://www.cir-safety.org/supplementaldoc/cir-procedures), the Expert Panel shall determine whether each ingredient, under each relevant condition of use, is safe, safe with qualifications, unsafe, or there are insufficient data or information to make a determination of safety. Upon making such a determination, the Expert Panel shall issue a conclusion and/or announcement.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson || (PR): Preethi Raj || (JZ): Jinqiu Zhu

ONE HUNDRED FIFTY-SIXTH MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

December 7-8, 2020

Microsoft Teams Virtual Meeting

Expert Panel Members

Wilma F. Bergfeld, M.D., Chair

Donald V. Belsito, M.D.

David E. Cohen, M.D.

Curtis D. Klaassen, Ph.D.

Daniel C. Liebler, Ph.D.

Lisa A. Peterson, Ph.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Paul W. Snyder, D.V.M., Ph.D.

Liaison Representatives

Consumer

Thomas Gremillion, J.D.

Industry

Alex Kowcz, M.B.A.

Government

Nakissa Sadrieh, Ph.D.

_____

Adopted (Date)

_____

Wilma F. Bergfeld, M.D.

Cosmetic Ingredient Review

Commitment & Credibility since 1976

CIR Staff

Administration
Bart Heldreth, Ph.D. - Executive Director

Monice Fiume, M.B.A. - Senior Director

Carla Jackson - Administrative Coordinator

Subject Matter Expertise
Jinqiu Zhu, Ph.D., D.A.B.T, E.R.T. - Toxicologist

Analysis
Christina L. Burnett, M.S.E.S - Senior Scientific Analyst

Wilbur Johnson, Jr., M.S. - Senior Scientific Analyst

Preethi S. Raj, M.S. - Senior Scientific Analyst

Priya Cherian - Scientific Analyst

Information Services
Kevin Stone Fries, M.L.S. - Information Services Manager

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Others Present at the Meeting

Irina Agro	**schülke, inc**
Christina Akintoye	**Honye's Skincare**
Don Bjerke	**Procter & Gamble**
Sophia Chen	**Sandream Impact**
Wei Chen	**Mast Global**
Anne Corriou	**GIVAUDAN**
Cheng-Ji Cui	**J&J Consumer**
Vivek Dadhania	**Bath & Body Works**
Carol Eisenmann	**PCPC**
Stefan Fellner	**Premium Organic**
Janet Finnerty	**DKSH North America, Inc**
Tracy Guerrero	**ACC/SEHSC**
Tony Larkman	**ATTIA Ltd**
Martha Leal	**Mary Kay INC**
Linda Loretz	**PCPC**
Rajendra Patil	**Colpal India**
Phillip Prather	**ATTIA**
Maryann Rodas	**The Estee Lauder Companies**
Alexandra Scranton	**Women's Voices for the Earth**
Richard von Stein	**L'Oreal USA**
Jan Summers	**Sanofi**
Silpa Vincent	**Hatchbeauty Brands**
Brian Wall	**Colgate-Palmolive**
Michael Wyatt	**FDA**
Merle Zimmermann	**American Herbal Products Association**

MINUTES FROM THE 156th EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY MEETING

CHAIRMAN'S OPENING REMARKS

Dr. Bergfeld welcomed Dr. David E. Cohen, new Panel Team leader, to the Panel. This position was previously held by Dr. James Marks, Jr., whose retirement became effective after the September 2020 Panel meeting. She also welcomed all attendees to the 156th meeting of the Expert Panel for Cosmetic Ingredient Safety. Dr. Bergfeld stated that 15 ingredient reports were reviewed in Teams on the preceding day. Most of the reports reviewed are new draft reports, and 7 of the 15 relate to botanical ingredients. Some data relating to ingredient use concentrations were received late and will be considered at today's meeting. Dr. Bergfeld thanked the CIR staff and the Council for their support throughout the review process.

APPROVAL OF MINUTES

The minutes of the September 14-15, 2020 (155th) Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the Cosmetic Ingredient Review program. He also noted that 2020 has been a remarkably interesting year for all, CIR included. For the first time, the meetings of the Expert Panel were 100% virtual and the Panel also got a new team leader. Dr. Heldreth again welcomed Dr. Cohen, who stepped into the team leader role at this meeting. The consensus was that he had done a marvelous job.

Dr. Heldreth mentioned that he has always enjoyed learning. Since he joined CIR in 2010, he felt like he has learned so much from the experts at the table. He felt extremely fortunate to have such wonderful teachers, and, he was not the only one who felt this way. Indeed, in 2020, Dr. Bergfeld was awarded the Cleveland Clinic Foundation Dermatology Teacher of the Year Award, the American Academy of Dermatology's Thomas Pearson Memorial Education Award, and the Accreditation Council for Graduate Medical Education's Parker J. Palmer Courage to Teach Award. Dr. Heldreth concluded by reiterating his gratitude to each and every person present for making this Panel what it is.

Final Safety Assessments

Wheat Ingredients

The Expert Panel for Cosmetic Ingredient Safety issued a final report with the conclusion that the following 21 wheat-derived ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment:

Triticum Aestivum (Wheat) Flour Lipids
Triticum Aestivum (Wheat) Germ Extract
Triticum Aestivum (Wheat) Seed Extract
Triticum Monococcum (Wheat) Seed Extract
Triticum Spelta Seed Water
Triticum Turgidum Durum (Wheat) Seed Extract*
Triticum Vulgare/Aestivum (Wheat) Grain Extract*
Triticum Vulgare (Wheat) Bran
Triticum Vulgare (Wheat) Bran Extract
Triticum Vulgare (Wheat) Bran Lipids
Triticum Vulgare (Wheat) Flour Extract
Triticum Vulgare (Wheat) Flour Lipids
Triticum Vulgare (Wheat) Germ
Triticum Vulgare (Wheat) Germ Extract
Triticum Vulgare (Wheat) Germ Powder*
Triticum Vulgare (Wheat) Germ Protein
Triticum Vulgare (Wheat) Gluten
Triticum Vulgare (Wheat) Gluten Extract
Triticum Vulgare (Wheat) Kernel Flour
Triticum Vulgare (Wheat) Seed Extract
Wheat Germ Glyceride

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

However, the Panel also concluded that the available data are insufficient to make a determination of safety on the following 6 wheat-derived ingredients:

Triticum Aestivum (Wheat) Leaf Extract**	Triticum Vulgare (Wheat) Protein
Triticum Aestivum (Wheat) Peptide**	Triticum Vulgare (Wheat) Sprout Extract
Triticum Monococcum (Wheat) Stem Water	Triticum Vulgare (Wheat) Straw Water**

***There are currently no uses reported for these ingredients.*

The data needed to determine the safety of these ingredients are:

- Composition and impurities data
    - If significantly different from the ingredients considered safe: dermal irritation and sensitization data at maximum use concentration are needed

The Panel noted that it had previously concluded that Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten were safe for use in cosmetics when formulated to restrict peptides to an average molecular weight of 3500 Da or less. This conclusion was in response to reports of type 1 (IgE-mediated) immediate hypersensitivity reactions that occurred in sensitized individuals following exposure to cosmetic products that contained one of these two ingredients with molecular weights greater than this limit. However, based on the available information, none of the wheat-derived ingredients in this report are hydrolyzed and most are not even proteins. Coupled with lack of reports to the contrary or experience with such reactions to these ingredients in the clinical setting, concern over such reactions to these ingredients was mitigated. If the protein ingredients in this report are hydrolyzed in processing, then the Panel needs to be made aware of these methods of manufacturing to further assess the safety of these ingredients.

Polysilicone-11

The Panel issued a final report with the conclusion that Polysilicone-11 is safe in the present practices of use and concentration described in the safety assessment. A supplier reported that this ingredient is the product of a pure addition reaction, forming no impurities and resulting in no residual monomers. The safety of this ingredient was supported by sufficient sensitization/irritation data, and lack of adverse clinical reports. In addition, as this ingredient is reported to have a large molecular weight, it is unlikely to penetrate the skin, mitigating the concern for systemic toxicity. According to 2020 VCRP data, Polysilicone-11 is reported to be used in 440 formulations, 432 of which are leave-on formulations. Results of the concentration of use survey conducted by Council in 2018, and updated in 2019, indicate Polysilicone-11 is used at a maximum concentration of up to 19.9% in other skin care preparations.

According to 2020 VCRP data, Polysilicone-11 is reported to be used in 440 formulations, 432 of which are leave-on formulations. Results of the concentration of use survey conducted by Council in 2018, and updated in 2019, indicate Polysilicone-11 is used at a maximum concentration of up to 19.9% in other skin care preparations.

Glycerin Ethoxylates

The Panel issued a final report with the conclusion that the following 8 glycerin ethoxylate ingredients are safe in the present practices of use and concentration as described in the safety assessment, when formulated to be non-irritating:

Glycereth-3 Glycereth-12	Glycereth-7 Glycereth-18	Glycereth-8 Glycereth-20
Glycereth-26	Glycereth-31	

The Panel deemed the relevant safety data to be sufficient, as well as the complete experimental details received for previously-submitted HRIPT summaries, to be sufficient. Mild erythema reactions observed during induction were considered indicative of irritation potential.

Tentative Safety Assessments

Amino Acid Diacetates

The Panel issued a tentative report with the conclusion that Tetrasodium Glutamate Diacetate is safe in cosmetics in the present practices of use and concentration described in the safety assessment. However, the Panel concluded that the data were insufficient to make a determination of safety for Beta-Alanine Diacetic Acid. The additional data needed to determine safety for this cosmetic ingredients are:

- Method of manufacturing
- Composition and impurities
- Concentration of use
- Dermal irritation and sensitization data at maximum expected use concentration
- 28-day dermal toxicity data
    - If positive, developmental and reproductive toxicity and genotoxicity data may be needed

The Panel found that the systemic toxicity data, including developmental and reproductive toxicity studies, acute and subchronic toxicity studies, and dermal irritation and sensitization studies in this report were sufficient for assessing safety for reported cosmetic uses of Tetrasodium Glutamate Diacetate. The Panel noted that Tetrasodium Glutamate Diacetate is slowly absorbed through the gastrointestinal tract: dermal absorption is likely to be even slower. The Panel also noted the lack of carcinogenicity data and was concerned about the report by a supplier that Tetrasodium Glutamate Diacetate may contain a salt of nitrilotriacetic acid, a 2B carcinogen according to the International Agency for Research on Cancer; however, this concern was mitigated by the multiple genotoxicity studies that were negative, and the low use concentrations of this ingredient in leave-on products.

Acetyl Hexapeptide-8 Amide

The Panel concluded that Acetyl Hexapeptide-8 Amide is safe in cosmetics at concentrations up to 0.005%, and that the available data are insufficient for evaluating safety at higher concentrations. A revised tentative report with this conclusion was issued.

Acetyl Hexapeptide-8 Amide (CAS No. 616204-22-9) is defined as the product obtained by the acetylation of hexapeptide-8 in which the C-terminus is an amide. Initially, the title of this safety assessment was Acetyl Hexapeptide-8 and Acetyl Hexapeptide-8 Amide. However, it has since been determined that Acetyl Hexapeptide-8 Amide is synonymous with Acetyl Hexapeptide-8, acetyl hexapeptide-3, Acetyl Hexapeptide-24, and Acetyl Hexapeptide-24 Amide. The sequence for this acetylated and amidated peptide is Ac-Glu-Glu-Met-Gln-Arg-Arg-NH_2.

The Panel noted that the available in vitro and in vivo data indicate that Acetyl Hexapeptide-8 Amide may have drug activity (i.e., anti-wrinkle effect) by exerting an effect on type I and type III collagen in the dermis at a concentration of 10%. The Panel also stated their awareness of a consumer product purported to contain 10 to 30% Acetyl Hexapeptide; however, whether this product is a drug or cosmetic remains unknown. The Panel recognizes that Acetyl Hexapeptide-8 Amide is used in leave-on cosmetic products at concentrations up to 0.005%, based on vetted information sources, and that a drug effect (i.e., anti-wrinkle effect) on the dermis would not be likely at this low concentration. Nonetheless, the Panel acknowledges that the drug effect may be apparent at higher use concentrations.

The Panel noted the absence of systemic toxicity and detailed genotoxicity data on Acetyl Hexapaptide-8 Amide. Still, concern over the lack of these data was mitigated, after considering the peptide structure of this ingredient, the associated low partitioning coefficient of -6.3 (percutaneous absorption unlikely), and the low maximum use concentration of 0.005% in leave-on cosmetic products. On the subject of potential percutaneous absorption, the Panel also noted differing degrees of reported skin penetration by Acetyl Hexapeptide-8 Amide with in vitro models. The Panel felt that studies that utilized liquid chromatography with tandem mass spectrometry to measure the peptide were most dependable, and noted that these studies indicated minimal skin penetration.

Finally, the Panel agreed that a no-observed-adverse-effect-level (NOAEL) for type I and type III collagen synthesis would be needed in order to evaluate the safety of Acetyl Hexapeptide Amide in cosmetic products at concentrations > 0.005%.

Basic Brown 17

The Panel issued a tentative report with the conclusion that Basic Brown 17 is safe for use in hair dye products; however, the data are insufficient to make a determination of safety for use in other cosmetic product types.

The additional data needed for use in other cosmetic product types are:

- Concentration of use and reported function for the non-hair coloring product uses that were reported in the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database
- Dermal irritation and sensitization data at maximum use concentrations

Basic Brown 17 is reported to function as a direct, non-oxidative hair dye in hair coloring products. The Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures. The Panel considered concerns that such self-testing might induce sensitization, but agreed that there was not a sufficient basis for changing this advice to consumers at this time.

The Panel expressed concern over the mixed results in the genotoxicity studies and the lack of carcinogenicity studies. However, the Panel noted that the toxicokinetic studies show that Basic Brown 17 does not absorb through the skin and that a conservative margin of safety calculation yielded a result of 1000. These findings, coupled with the short exposure time as a rinse-off product, helped mitigate these concerns.

Methicones

The Panel issued a revised tentative amended report, with a split conclusion, for these 30 ingredients. Specifically, the Panel concluded that these ingredients are safe as used in the present practices of use and concentration as described in this report, when formulated to be non-irritating; however, the Panel also concluded that the data are insufficient to support the safety of products containing these ingredients when applied via airbrush technology.

Amino Bispropyl Dimethicone
Aminopropyl Dimethicone
Amodimethicone
Amodimethicone Hydroxystearate*
Behenoxy Dimethicone
C20-24 Alkyl Dimethicone
C20-24 Alkyl Methicone*
C24-28 Alkyl Dimethicone*
C24-28 Alkyl Methicone
C26-28 Alkyl Dimethicone
C26-28 Alkyl Methicone*
C30-45 Alkyl Dimethicone
C30-45 Alkyl Methicone
C30-60 Alkyl Dimethicone
C32 Alkyl Dimethicone*
Capryl Dimethicone
Caprylyl Methicone
Cetearyl Methicone
Cetyl Dimethicone
Dimethicone
Dimethoxysilyl Ethylenediaminopropyl Dimethicone
Hexyl Dimethicone
Hexyl Methicone*
Hydroxypropyldimethicone*
Methicone
Stearamidopropyl Dimethicone*
Stearoxy Dimethicone
Stearyl Dimethicone
Stearyl Methicone
Vinyl Dimethicone

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

The Panel was made aware at this meeting that Dimethicone and Methicone are used in consumer products which are applied via aerosolized airbrush devices. The Panel considered information suggesting that airborne particles resulting from airbrush delivery are respirable, and, consequently, that more information on particle size distribution and the present concentrations of use for these ingredients in airbrush products is needed. Additionally, the Panel discussed how the types of airbrush products these ingredients are used in would affect the exposure duration and frequency (e.g., daily, brief foundation application, compared to periodic, but longer suntan spray exposure). Thus,

the Panel reasoned that these additional data, including more inhalation toxicity data for respirable particles, were warranted to make a determination of safety for this product category.

Papaya Ingredients

The Panel issued a tentative report for public comment with the conclusion that the available data are insufficient to make a determination that the following 5 *Carica papaya*-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Carica Papaya (Papaya) Fruit	Carica Papaya (Papaya) Fruit Juice	Carica Papaya (Papaya) Leaf Extract
Carica Papaya (Papaya) Fruit Extract	Carica Papaya (Papaya) Fruit Water*	

**not reported to be in use*

In order to determine safety for Carica Papaya (Papaya) Fruit, Carica Papaya (Papaya) Fruit Extract, Carica Papaya (Papaya) Fruit Juice, and Carica Papaya (Papaya) Fruit Water, the Panel has requested phototoxicity/photosensitization data. These data have been requested due to the fact that the existing studies in the report regarding phototoxicity/photosensitization on Carica Papaya (Papaya) Fruit Extract include an SPF 50 sunscreen lotion as part of the test formulation. It is unknown whether the ingredients in this sunscreen formulation would inhibit the potential phototoxicity/photosensitization of Carica Papaya (Papaya) Fruit Extract. In lieu of phototoxicity data on the papaya-derived fruit ingredients, the Panel would also accept a clarification on the specific ingredients of the SPF 50 lotion in the existing phototoxicity/photosensitization assays. In addition, in order to determine safety for Carica Papaya (Papaya) Leaf Extract, the Panel has requested genotoxicity, irritation, sensitization, and phototoxicity/photosensitization data.

Polyquaternium-6

The Panel issued a tentative report for public comment with the conclusion that Polyquaternium-6 is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel noted that most of the safety test data in this report are on high molecular weight Polyquaternium-6 (42%, MW 150,000 Da, 6.5% monomer content). It was agreed that, overall, the available data are not indicative of any safety concerns relating to skin sensitization, systemic toxicity, or other toxicity endpoints, while acknowledging the polymer and monomer content of the test substance administered. The Panel considered the limited, negative skin sensitization/photosensitization data in this safety assessment, but noted that potential concerns relating to systemic exposure, in the absence of additional data, would be mitigated because this ingredient would not be percutaneously absorbed.

The Panel discussed the issue of incidental inhalation exposure from the use of Polyquaternium-6 in hair sprays (pump sprays) at maximum use concentrations up to 0.5%. The Panel stated that droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of Polyquaternium-6. Finally, the Panel cautions that products containing Polyquaternium-6 should be formulated to avoid the formation of nitrosamines.

Tris(Tetramethylhydroxypiperidinol) Citrate and Hydroxy Tetramethylpiperidine Oxide

The Panel issued a tentative report concluding that these 2 ingredients are safe as used in the present practices of use and concentration in cosmetics as described in the safety assessment. The Panel determined that the low maximum reported dermal concentration and high NOAEL of 150 mg/kg bw/d Tris(Tetramethylhydroxypiperidinol) Citrate (at 97.3% purity) from a 90-d dermal toxicity study, as well as robust toxicological data for both ingredients, were sufficient to support safety.

Insufficient Data Announcements

Barley Ingredients

The Panel issued an Insufficient Data Announcement (IDA) for the following 16 barley-derived ingredients:

Hordeum Distichon (Barley) Extract
Hordeum Distichon (Barley) Seed Flour
Hordeum Vulgare Extract
Hordeum Vulgare Flower/Leaf/Stem Juice
Hordeum Vulgare Juice
Hordeum Vulgare Leaf Extract
Hordeum Vulgare Leaf Juice
Hordeum Vulgare Leaf Powder
Hordeum Vulgare Leaf/Stem Powder
Hordeum Vulgare Powder
Hordeum Vulgare Root Extract
Hordeum Vulgare Seed Extract
Hordeum Vulgare Seed Flour
Hordeum Vulgare Seed Water
Hordeum Vulgare Sprout Extract
Hordeum Vulgare Stem Water

The additional data needed to determine safety for these cosmetic ingredients are:

- 28-day dermal toxicity data on the whole plant extracts Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
    - If positive, developmental and reproductive toxicity and genotoxicity data may be needed
    - Alternatively, acceptable evidence of safe use as a food for ingredients derived from the flower, leaf, stem, and root
- Dermal irritation and sensitization data at maximum concentration of use for the whole plant extracts Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract

Equisetum arvense Ingredients

The Panel issued an IDA with the following data requests on the *Equisetum arvense*-derived ingredients that are listed below:

Equisetum Arvense Juice, Equisetum Arvense Leaf Extract, Equisetum Arvense Leaf Powder, and Equisetum Arvense Powder

- Method of manufacture, impurities, and composition data

Equisetum Arvense Extract

- Skin irritation and sensitization data at maximum concentration of use

The Panel also noted that hair loss was observed in an oral dosing study in which Sprague-Dawley rats were fed a 4% *Equisetum arvense* powder in a cholesterol diet for 14-d. However, they also noted no obvious clinical signs in another study in which F344 rats were fed *Equisetum arvense* (hot water extract of powder) at concentrations up to 3% in a basal diet for 13 wk.

Melaleuca alternifolia (Tea Tree) Ingredients

The Panel reviewed the assessment of 8 *Melaleuca alternifolia* (tea tree)-derived ingredients as used in cosmetics for the first time, and found the data were insufficient to determine safety of these ingredients.

Melaleuca Alternifolia (Tea Tree) Extract
Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract
Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Oil
Melaleuca Alternifolia (Tea Tree) Leaf
Melaleuca Alternifolia (Tea Tree) Leaf Extract
Melaleuca Alternifolia (Tea Tree) Leaf Oil
Melaleuca Alternifolia (Tea Tree) Leaf Powder
Melaleuca Alternifolia (Tea Tree) Leaf Water

The Panel noted that the majority of the data included in the report were on tea tree oil; this name is not an International Nomenclature Cosmetic Ingredient (INCI) name. Although the report was robust with data for tea tree oil, and the Panel considered these data relevant to the oil ingredients in the report (i.e., Melaleuca Alternifolia (Tea

Tree) Flower/Leaf/Stem Oil and Melaleuca Alternifolia (Tea Tree) Leaf Oil), it was not clear to the Panel whether those data are also relevant to the non-oil ingredients. Accordingly, the Panel issued an IDA requesting the following:

- Methods of manufacture, composition, and impurities data for the non-oil ingredients named above
    - if these are significantly different from data on the oils, then irritation and sensitization data for Melaleuca Alternifolia (Tea Tree) Extract at the expected maximum concentration of use, and other toxicity endpoints, specifically to include genotoxicity data, may be needed

***Portulaca oleracea* Ingredients**

The Panel issued an IDA for these 4 *Portulaca oleracea*-derived ingredients:

Portulaca Oleracea Extract
Portulaca Oleracea Flower/Leaf/Stem Extract
Portulaca Oleracea Juice
Portulaca Oleracea Water

The data needed to determine safety include:

- Clarification on the current maximum concentration of use
- A 28-d dermal toxicity study at the maximum concentration of use (preferably with the ingredient in an hydroalcoholic solvent)
    - If these data are positive, further systemic toxicity data may be needed

- An Ames test (preferably with the ingredient in an hydroalcoholic solvent)

***Saccharum officinarum* (Sugarcane) Ingredients**

The Panel issued an IDA for the following 4 *Saccharum officinarum* (sugarcane)-derived ingredients:

Saccharum Officinarum (Sugarcane) Bagasse Powder
Saccharum Officinarum (Sugarcane) Extract
Saccharum Officinarum (Sugarcane) Juice Extract
Saccharum Officinarum (Sugarcane) Wax

In order to arrive at a conclusion of safety for this ingredient group, the Panel requested:

- Sensitization/irritation data for Saccharum Officinarum (Sugarcane) Extract at the maximum concentration of use

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: February 16, 2021
Subject: Draft Revised Hair Dye Epidemiology Document for Panel Review

Enclosed is an updated draft of the Expert Panel Resource Document – Hair Dye Epidemiology (*hdepi032021rep*), as well as the transcripts of the discussion of the Resource Document at the previous Expert Panel meeting (*hdepi032021min*). The previous draft was finalized by the Panel at the December 2018 meeting.

At the December 2018 meeting, the Panel determined to continue monitoring upcoming epidemiological data on the link between personal use of hair dyes and cancer risk and the conclusion of the document would be re-evaluated based upon the new information on a regular period basis. Since then, 10 new epidemiological studies, including 1 genetic polymorphism study, 4 case-control studies, 2 meta-analysis studies, and 3 prospective cohort studies, have been discovered. The association between hair dye use and risk for various cancer types was investigated, such as breast cancer, leukemia, brain cancer, testicular cancer, non-Hodgkin's lymphoma, follicular lymphoma, and so on. These additional studies are incorporated herein, highlighted in yellow, for the Panel's consideration.

The Panel should review this Document, especially noting the data presented in the new studies. If this Document is in agreement with their thinking, it should be finalized and used to replace the version currently posted on the Findings & Resources Documents page (https://www.cir-safety.org/cir-findings). If the Document is not considered to be ready for finalization, specific needs/edits therein should be made evident.

Day 1 of the April 10-11, 2017 Expert Panel Meeting – Dr. Marks Team

DR. MARKS: Now we'll go back to hair dye. Something that Ivan and I are very interested in. Do you want any, you made, some, a few comments, changes in red. A lot of it has to do with obviously cancer, and after you make your comment, Ivan, I'd like obviously Tom to react and then anybody else. Ron and Ron. So, Ivan, do you want to bring us up to date on that? And that's administrative page 35.

DR. BOYER: So, for hair dye, we've been monitoring the literature, looking for papers that might be relevant for updating this particular document, which we have posted online, which we refer to through a link that's incorporated into our safety assessment reports when it's appropriate. And it's been a while since we've updated anything. A few papers have shown up in the literature that seem to be relatively inconsequential, as far as the bottom line is concerned for this particular document. But we thought that, at this point, it'd be a good time to go ahead and incorporate those few papers that we have in this particular revision. And I guess to get the panel's feedback on whether or not simply accepting those changes is adequate, or if you see anything in there that might warrant some additional attention at this point.

DR. SHANK: I think you've done a great job. I don't have any change.

DR. SLAGA: I completely agree.

DR. MARKS: Okay. Sounds like we endorse the changes, Ivan…

DR. HILL: Yeah, I just had a couple of questions. When you mention, it's reference 15, it's the Chang et al, in cancer case control. Would it be appropriate to add any short sentence fragment on the nature of the association? When it says there's an association between this, that or the other, is there anything that can be? Do you know where I'm talking about here, it's exactly where the, search on associations. I usually highlight this sort of thing.

DR. SHANK: Is it page 41? On that table?

DR. HILL: Yes. I think that's it. That's exactly it. It's in the table where it's mentioned. I think that's the same reference where they re-analyzed what appeared to be the same data set. So it was more than 2007, is that the one? I'm not sure. Hold on. Yeah. John 2009 versus Morton 2007. I think it's the same data. Or that might be a different one. No that's a different one. That's a different one.

DR. BOYER: So, when you're asking for additional information on what the nature of the association, do you mean, for instance, the odds ratio that they may have calculated?

DR. HILL: It says an association between ever/never use of hair dyes, and the negative NHL was reported. That doesn't tell me anything. Just there was an association.

DR. BOYER: All of these studies have been summarized in a little bit more detail in the text of the document.

DR. HILL: Yeah

DR. BOYER: We try to keep it fairly short, and consistent as far as the information that we presented for each of the studies summarized. But I can take another look at it. The nature of the association is, at this point, you know, we've got these two different varieties of lymphomas. And one of them, there was a statistically-significant association that's probably represented by an odds ratio. None of the odds ratios exceed about two or so. So they're fairly small, and given the confounding factors typical in those types of studies, they're…

DR. HILL: I had been looking for something simpler, which was, it increased the odds of the cancer, or it decreased.

DR. BOYER: Oh, I see what you mean.

DR. HILL: Maybe that's implicitly obvious. That's so obvious, it couldn't have been that. It must have been a little more description but in there…

DR. BOYER: Okay

DR. HILL: But it sounds like there is no short encapsulation. From what you're saying. Sorry, I interrupted you. Didn't mean to…

DR. BOYER: That's fine. I'll take another look at it and see if we can include something a little more informative, without going into great detail.

DR. HILL: And similarly, just to enlighten, again, the reader can go out, but they have to go out and look at references, what the nature of the STAR 10 mutant of that N-acetyl transferase type one is the NAT 10. What exactly is the STAR 10? I actually had difficulty finding. But I think it's out there, I just didn't follow-up and finish before I got here. I was looking at this like two weeks ago. It was on my punch list, but I didn't get that far.

DR. BOYER: Mm hmm. Okay. I'll do that.

DR. MARKS: Okay. Any other comments about the hair dye boilerplate?

DR. BERGFELD: Was that to be an edit? And then it will go up on the website? Was that to be an edit?

DR. MARKS: Yeah. I think we'll have a discussion tomorrow.

DR. BERGFELD: Okay

DR. MARKS: And Ron Hill, you can bring it up. It sounds like Ivan, you'll take a look at it and see how it can be changed a little bit. But I didn't get a sense from Tom or Ron Shank that there was concern about this.

DR. SLAGA: My only comment about that would be, it's so weak, that you have to be careful how you state it. I mean you don't want it to come across like you're increasing cancer.

DR. HILL: Point well taken.

DR. SLAGA: So, the words, I like the way you have it.

DR. HILL: Okay. I mean, that's fine.

DR. MARKS: Okay. That's important, Tom. So it sounds like, Tom, as our cancer expert, would say leave it the way it is. Don't worry about smithing it. And we'll see what the Belsito team says tomorrow. Am I interpreting correct, Tom? Is that okay with you, Ron Hill?

DR. HILL: Yes. I still think a short description of what NAT 10 is belongs in there. And the STAR 10 allele. And also, similarly you've got arylamine acetyltransferases that can function to activate or de-activate arylamines. I've never encountered an instance of activating by acetyltransferases acetylation. And Ron Shank might have a thought on this, but acetylation, as far as I've seen, is always inactivating in terms of abolishing toxicity. So that's why you look at fast acetylaters versus slow acetylaters. In terms of certain drugs that have aniline-type nitrogens, or can have aniline-type nitrogens generated. That the acetylation, which is what the acetyltranferase is catalyzed, invariably deactivating.

DR. BOYER: So it sounds like what you're suggesting are basically some clarifications that wouldn't take much in terms of editing.

DR. HILL: No, in that particular case it's just function to activate or deactivate. I was sort of suggesting that we don't need activate, just deactivate. But I wanted to see if any of the others were aware of any cases where they saw that acetylation serve to activate. I've never encountered such.

DR. MARKS: I assume from a procedural point of view the Council, the Scientific Committee, will have some comments. And we're going to look at these documents again. Boilerplates with that in light.

DR. EISENMANN: Right, and this one is the Hair Color and Technical Committee that will look at it.

DR. MARKS: We'll have another look at this before it gets posted, I suspect. Unless that committee says everything looks fine and we can proceed.

DR. GILL: We were hoping to have a presentation at the June meeting from someone from that technical committee.

DR. MARKS: Okay.

DR. GILL: We've just decided to get this out earlier to get the thinking going.

DR. SADRIEH: I just have a question. So, I just want to understand that an increase in the arteries show two is not to be considered an increase in cancer? Is that what you're concluding? That an increase is not…

DR. SHANK: Statistically, it comes out so weakly, that most people I know consider it not to be a positive effect. It's a weak association is the only way I can describe it. It doesn't make it, I think if you use the word increase, it sounds like it's really increasing. That is questionable.

DR. SADRIEH: Okay. From one to two is not an increase. Is that? I mean, like a three would be an increase? What would be an increase then?

DR. SHANK: The change is insignificant.

DR. BOYER: You also want to look at the confidence interval. I mean if you have a two, and you have a confidence interval that doesn't include one, or the minimum is not far from one, then you would consider that to be a very weak association. On the other hand, if you have an odds ratio of 10, 11, 12 and so forth, and an odds ratio that does not include one, that exceeds one proportionally, then that would be a clear indication that there's an association. Generally, that's how epidemiological studies are interpreted. And there's good reason for that. There's a good argument that can be made to support that perspective, that way of interpreting those kinds of studies.

DR. MARKS: Thank you. That was helpful. Refreshed my memory on statistics 101. Any other comments on hair dye boilerplate? If not, then, tomorrow I'm just gonna mention that the format, the changes are fine with our team.

Day 1 of the April 10-11, 2017 Expert Panel Meeting – Dr. Belsito Team

DR. BELSITO: Hair dye. What page, and this is in admin.

DR. LIEBLER: 36.

DR. BELSITO: So with the bladder cancer, I mean again there's so much with these epi studies. There was that women who were college grads were more likely among hair dye users to have bladder cancer. I mean when you broke them out. And, again, were these studies controlled for smoking and other contributing factors, do we know? In this study by Ross, et al, 2012, a population based study -- Oh, no that wasn't the one. It was the one in New Hampshire, Vermont, right? Yeah. So in the Koutros 2011 study, the study in Maine, Vermont, New Hampshire, the finding was an increase in bladder cancer with permanent hair dye use in a sub group of women with a college degree. But not dose response for color duration of use, or total lifetime uses.

And then the NAT2 phenotype was associated with a suggestive but not statistically-significant increase when college degreed women were stratified by education.

I mean I just point that out because, looking back at my childhood in the 50s and 60s, the mothers who went to college seemed more likely to be smokers, at that point in time, than the women who did not go to college in the 40s, because they were cool, educated, college women and sophisticated, and smoking was sophisticated. So, I mean, we know smoking is a risk for bladder cancer. So, in a lot of these epi studies, it just would be nice to get a sense of how well these were controlled. And then you have that whole issue of hair dye use pre 1980, post 1980, in terms of cancers.

Because there's no consistent trend, but then the data is also, it's the same with breast cancer. The Finnish study, there was an increase in odds of breast cancer in women who ever used hair dye, compared to those who never used hair dye. And it's a significant trend in the odds ratio for cumulative use of hair dyes. And that's coming out of Finland, where I would presume most women aren't using the same color hair dyes that the Italian women would be using. They're going to be much lighter colored hair dyes, if not blondish hair dyes.

It would be nice to see, and to report when we're doing this, whether they analyzed for other confounding factors between the control groups. What was the difference in bladder cancer among those who never used a hair dye? Did they smoke or not smoke? Did they even look at that? I mean otherwise I thought it was fine. I have no comments. We can continue to use it with the updates, but it's just that as I read through it, the idea of any confounding factors that might affect these cancers was never even mentioned.

DR. BOYER: It is pretty much standard practice for people who do epidemiological studies to at least do some sort of an analysis for the confounding variables. But they usually lump them together, so it's unlikely that smoking would be isolated as a single confounding factor in any one of these studies. But we can certainly bring forward --

DR. BELSITO: Just a brief statement as to whether confounding factors were looked at at all. They usually are, but not always.

DR. LIEBLER: I'm assuming these little paragraphs are mostly taking from the abstract from the papers.

DR. BOYER: No, actually they are our own.

DR. LIEBLER: I don't mean literally word for word, but you're distilling this from the main conclusions from the abstracts?

DR. BOYER: At least for the ones that I summarized, I've looked at the whole paper. And we rated the quality of the paper, let's put those plusses, double plusses, triple plusses.

DR. BELSITO: Right, four plusses.

DR. LIEBLER: The confounders are usually not mentioned in the abstract. But usually they are discussed in the discussion. And I'm sure you've looked at that. So that's there if you want it.

I took a very different approach to this document, maybe it was because I was near the end of my preparation, but I basically started with okay, for hair dyes, we basically take the position right now that there are no convincing data that support the causative relationship between hair dyes and cancers. So I'm looking at the new changes to see if any of those changed that conclusion. My assessment no. So we can update it, but doesn't change the conclusion.

DR. BELSITO: Yeah, fine. And I guess my point was a mention when we update it that confounding factors were or were not looked at in the report.

DR. SYNDER: Was that considered in your scoring scale, a one plus, two plus, three plus, whether they looked at confounding?

DR. BOYER: Whether they looked at confounding, no.

DR. SYNDER: Probably should. I have kind of a silly comment, but in the intro or something you should identify bladder cancer as urinary bladder cancer, not gall bladder cancer or something else.

Day 2 of the April 10-11, 2017 Expert Panel Meeting – Full Panel

DR. MARKS: The next is a draft update of the expert panel hair dye epidemiology. Findings and --. There are actually a number of changes in there. But our panel did like this also. So we'll mimic the Belsito team, at least in the previous drafts. We liked it.

DR. BERGFELD: Yeah. Belsito team. You liked it too?

DR. BELSITO: Yeah. I'm just trying to find out exactly where it is. Looking through dye and hair dye.

DR. MARKS: It's in page 35 in the Administrative tab there.

DR. BELSITO: Okay.

DR. MARKS: (inaudible)

DR. BELSITO: So, just off the top of my head, before I get to page 35. The one issue I had is, you know, yeah, the data is inconsistent. We say how we're looking at the data, yada yada yada. But, you know, there are some data coming out that are showing some linkages. So, for instance, in terms of, I believe it was bladder cancer in women in New Hampshire and Vermont, if they were college grads, that incidence was positive, if they weren't it wasn't. And just, you know, looking back at my own childhood in the 1950's and my parents. You know, my impression was that women who went to college smoked a lot more than women who didn't go to college in the 1950's. And I was just wondering how well these studies are controlled for other confounders that could influence the cancer's in question? And in our boilerplate, we never mention that. So, I mean, they are epi studies. They are very hard to control. But did they look at other confounding factors that might contribute to these cancers? And so I'm fine with the document. I don't think that, in consumers, there's any strong evidence to suggest carcinogenicity of these hair dyes. I would just like, as we're going through the documents, a simple statement as to how well they looked at potential confounders in these studies that might contribute to the specific cancer endpoints in question. You know, like, for instance, even the relationship between cosmetologists and bladder cancer, you know, there are studies that show that cosmetologists smoke more

than the general population. And then we know smoking is a risk for bladder cancer. So is it the hair dyes? Is it the other chemicals they use? Is it the smoking? Is it the combination of all of these? So, just a mention as to how well these studies were controlled for other confounders.

DR. BERGFELD: I'd like to make a comment. If you look at the references there, the references are in really strongly peer-reviewed journals.

DR. BELSITO: I understand.

DR. BERGFELD: I would think that those risk assessments, additional risk assessments, would have been made.

DR. BELSITO: Yeah. I mean, I think there should be --

DR. BERGFELD: A clarification would be well, but --

DR. BELSITO: -- at least a comment.

DR. BERGFELD: New England Journal, cancer. I mean, these are major.

DR. BELSITO: I'm not saying that they weren't.

DR. SLAGA: There's a lot of confounding issues and a good study that is peer reviewed, you know, that's one of the things they really look at. Are -- everything controlled for?

DR. BELSITO: Right. I understand. But we don't mention that in our --

DR. SLAGA: Yeah.

DR. BELSITO: -- reports. And I think just a one or two sentence mention that the following confounders were looked at.

DR. SLAGA: Yeah.

DR. LIEBLER: So, I think, even in the very best journals, the epidemiology is sometimes necessarily complicated by confounders. They can't be fully teased out and excluded, but need to be acknowledged, and are treated in their discussions.

DR. SLAGA: Right.

DR. LIEBLER: And this is going to be a case-by-case basis, where you might need to pull out something that appears interesting and potentially relevant from these discussions. And, Ivan indicated that he reviews the entire papers in preparing these. But I think it would be a good idea to consider, you know, looking at these carefully to see if there are any issues that were raised in a particular study that they said, you know, as possible confounder, we couldn't really resolve it. We think our conclusions are reasonably strong. But, and put the but in there for us.

DR. SLAGA: Right.

DR. BERGFELD: Good idea. I think that's a good editorial idea. Yeah. All right. Any further discussion. We have a next one?

Day 1 of the June 4-5, 2018 Expert Panel Meeting – Dr. Belsito Team

DR. BELSITO: Hair dye epidemiology, I guess that's the next one. That's also in admin, correct?

DR. HELDRETH: That's a separate book.

DR. BELSITO: Okay. Yes. I thought it looked fine. I had a couple of comments on PDF Page 3. The second line, third line -- so, let me see. It says, an odds ratio of 1 means that an exposure does not affect the odds of an outcome. RR of 1 means that there is no difference. I presume it's an odds ratio of less than 1. There is a less than sign missing there? Third line from the bottom, PDF Page 3.

DR. LIEBLER: I think odds ratio don't have a sign.

DR. BELSITO: Well, he's defining what it means. And odds ratio of less than 1, I believe, means an exposure does not affect; and of 1 means there's no difference; greater than 1 means the exposure my increase. He's defining what odds ratios mean. Read the sentence. So, I think it's an odds ratio of less than one means that an exposure does not. The 1 means there's no difference; and greater than 1 means it increases the risk. So, that needs to be changed.

And then on PDF, Page 9, the first paragraph. The sentence of the first paragraph, the one, two,

three, four, five, staring with, "Using a random effect model and the Duval and Tweedie's trim and fill procedure to adjust for publication bias in the presence of between studies heterogeneity." What does that mean?

DR. HELDRETH: I'm sorry, I was looking at another page. Where is that?

DR. BELSITO: PDF Page 9. The one, two, three, four, five, six -- six lines from the top, starting with using a random effects model. Are you with me?

DR. HELDRETH: Yes.

DR. BELSITO: Okay. Show procedure to adjust for publication bias in the presence of between studies heterogeneity. For publication bias for study heterogeneity? I don't understand what you're saying there.

DR. ZHU: That's the method they used in this paper, by this author, to do the meta-analysis.

DR. BELSITO: I understand the method, but the sentence makes zero sense to me. "For publication bias in the presence of between." Publication bias between studies? Publication bias because of heterogeneity of studies?

DR. ZHU: Okay. I think this method is used to evaluate the study's heterogeneity for different studies, epidemiology studies.

DR. HELDRETH: Right. But he's asking you -- the verbiage that's there isn't quite clear. Could you give us a better sentence?

DR. BELSITO: I guess my question is, what does the Duval and Tweedie's trim and fill procedure adjust publication bias for? For study heterogeneity? And then it says, "such meta-analysis showed." What is the bias that it adjusts for? I don't under that.

DR. HELDRETH: When they did the review of multiple studies, they excluded some studies. They had a bias, a rationale for why they excluded those studies, and possibly maybe that they're rationale was questionable. But that's to be assessed by the experts here.

DR. BELSITO: Right. I got the understanding that the trim and fill means they cut out some studies. I understand that. But for publication bias. I mean, what is in the presence of between studies heterogeneity? Publication bias because there was a lot of heterogeneity between the studies they put in the meta-analysis?

I don't understand what they're electing to trim. That sentence makes no sense to me and doesn't explain to me what that model is.

DR. ZHU: Sure. This is a model used by the author to do the meta-analysis.

DR. BELSITO: I understand. What I'm saying is, please look at what the model does and put it into a better sentence that makes it understandable as to what it's doing.

DR. ZHU: Sure.

DR. BELSITO: I had no other comments.

DR. LIEBLER: I just wanted to return to the odds ratio sentence because I think it was correct as originally written. So, this is again the bottom of Page 3 on the PDF. If we're talking about the same sentence, Don, I want to make sure; an odds ratio of one means that exposure does not affect the odds?

And if it's 1, that's exactly correct. If there's a lower risk of the outcome as a function of exposure, then that's when the odds ratio is less than 1, like .8 or .6 or .5. But as written, it was correct, so, it doesn't need to be "less than" added to that sentence.

DR. KLAASSEN: Well, the other aspect of these odds ratio is that they always give a confidence -- or a range. So, you can have an odds ratio of 1.5, but if the confidence interval is 0.9 to 2.3, it's not significantly different. It's kind of an over simplification because it's the odds ratio with the 95 percent confidence interval. For it to be significant, you not only have to have the odds ratio, but the 95 percent confidence limits greater than 1.0.

And there's a lot of them that are 1.4 that are not significantly different because you have the 1.4, and then your confidence interval goes from 0.8 to 2.3. So, then that's not significantly increased. Just so everybody realizes that.

DR. HELDRETH: Okay. Should we then add a small section about confidence intervals?

DR. KLAASSEN: I think for people that aren't familiar with that, and some people that are

reding this probably aren't.

DR. LIEBLER: I think as written, it does at least introduce what the odds ratio and relative risks are -- defines them clearly enough.

DR. KLAASSEN: Yes.

DR. LIEBLER: But then I agree with Curt's suggestion that perhaps we add a sentence or two at the end of the paragraph to explain that typically odds ratios are presented with calculated ranges based on the application of the appropriate statistical test.

DR. ZHU: Okay. Will do.

DR. BERGFELD: I was confused with just the tabulation of all these different studies. And the takeaway message is what? Is it presented here in the first couple of paragraphs, conclusion? I think it's in the first paragraph, in the beginning of the document. Because you end this document with the DNA repair enzyme genes and no summary, no discussion, no nothing.

DR. LIEBLER: You think we ought to move the conclusion paragraph to the end of the document?

DR. BERGFELD: I think like all of our documents -- this is a lot of information. Somewhere there has to be a summary in a few paragraphs, maybe, and a conclusion. I don't mind keeping the conclusion up front, but when I was reading this, I said, is this this conclusion, or is this the past conclusion? Because we've concluded the same thing in the past.

And then when it ends so abruptly. What is the information that we're passing on, risk, no risk? Maybe a risk?

DR. BELSITO: I agree with the conclusion part. I think the information is summarized under each of the cancer endpoints, prostate, bladder, breast, et cetera. And then at the end, you know, come to a little bit of a discussion that there have been reports of these various cancers associated with hair dyes. However, in reviewing all of the reports, there is no definite link between personal use and any of these cancers. And then our conclusion.

DR. BERGFELD: You agree that it should be added?

DR. BELSITO: Yeah. I mean, I see your point. I didn't see that when I was reading it because the conclusions were said, all at the end, for specific endpoints; but you're right. It could be taken that the conclusion up front was our prior conclusion and then at the end, we reviewed all of this and we haven't been able to make a conclusion. It's not the usual place that a conclusion is placed, at the beginning of a document.

DR. HELDRETH: For that conclusion that we're going to put at the end, is it the same verbiage that's already in the front? Or is there something different that the panel would like to say at the end?

DR. BELSITO: I think that the introduction should be what we had previously look at and what our prior conclusion was; and that since that time there had been a number of other reports, as outlined below, that have looked at these issues. And this is an update in our prior report, and a reconsideration of our conclusion.

DR. BERGFELD: With a date.

DR. BELSITO: With a date. And then go through all of this and then come back. And the conclusion can be the same; but it just points out that since 2014, or whenever it was that we last looked at this, we've now looked at all of the studies and still do not see a reason to change our initial conclusion.

DR. BERGFELD: Do you think there's a reason to put somewhere in the discussion that Dr. Naldi was asked to review these, that an expert reviewed it?

DR. BELSITO: I thought it was sort of clear there, but yeah, I mean, that's important.

DR. BERGFELD: I mean, it isn't just us looking at it, we've had an expert look at it.

DR. SNYDER: I agree with the Council's comment that we should change this to a guidance document.

DR. BERGFELD: Resource.

DR. SNYDER: Not from -- a guidance -- resource document from a guidance document. I think that the opening paragraph, which has been discussed here largely, should just be like one of our reports. It should be very succinct, like almost abstract form, and that language is exactly what we

incorporate into the report.

And before that, we say this document was last updated, and give the date; just like we do in our regular reports with a thorough literature search and consideration. Any new publications relevant to the epidemiology of the association between hair dye use and various cancers.

But I think that the opening thing should be exactly what we take, and that should go straight into our reports for hair dyes. And under that we can give the methodologies that we use to generate this resource document. And then followed by all of the brief summaries of all the individual studies.

DR. BERGFELD: And then a discussion/conclusion; it's the same format?

DR. SNYDER: Yeah. I think almost like one of our reports. I think that would be the most succinct way to handle it.

DR. HELDRETH: Okay. So, then the suggestion is that we expand this from the type of document -- the hair dye epidemiology document that it was -- and make it also have a boilerplate functionality to it?

DR. SNYDER: That's the recommendation. Then you can clearly see where the language comes that we take from our resource document; and then it's updated, and then it goes into our reports as they're published, subsequent to the most recent update.

MR. GREMILLION: I have a clarifying question. So, the expert is only between hair dye and breast cancer; is this doctor Naldi a dermatologist?

DR. BELSITO: Dr. Naldi is an epidemiologist in Bergamo Italy. I know him through his work in dermatology. He's considered a real expert epidemiologist. He consults for the Research Institute for Fragrance Materials, and a large epidemiologic study that they're sponsoring in Europe called the EDEN Group. So, he may be associated with the Department of Dermatology, I don't know, but his background is as an epidemiologist.

MR. GREMILLION: I also wanted to call attention to kind of an inconsistency I saw in his report. At the end of this document he says, "The available evidence linking hair dye use and breast cancer is limited but warrants further investigations." And earlier in the document, just half of that sentence, "The available evidence linking hair dye use and breast cancer is limited" period, is stated. I just felt like that was maybe a little bit of a mischaracterization of what he concluded.

DR. HELDRETH: I think the intent of -- and you know, I'm just trying to understand it from reading it myself. But I think the intent there was to lay out, well there may be some epidemiology studies here that maybe there's some sort of association or maybe there's not. But either way, epidemiology studies never give you cause and effect. Even if it came out with a strong odds ratio, that still would not mean that there's cause and effect. And there would need to be further study done to see if it's an actual causality.

DR. BELSITO: I actually took that as being, okay, here's the opening remark. It's limited, here's the data. And after looking at this limited data, here's my conclusion. It starts, the available evidence linking hair dye use and breast cancer is limited. It is limited. That evidence is limited. He's reviewed the evidence and his conclusion is that further studies are warranted.

MR. GREMILLION: Yeah. And the conclusion that further studies are warranted is a reason that -- implicit in that is that there is some evidence out there that would make you want to look for more evidence.

DR. BELSITO: Usually, when you say further studies are warranted, in science, it's because there's no definite data. It's that the studies that exist are limited, they don't conclude one way or the other, and therefore, more information is needed.

DR. SNYDER: Because the effect could be a compounding effect and have nothing to do with hair dyes. And so, I think that's what he's alluding to.

MR. GREMILLION: Sure, but to say the available evidence is limited, but warrants further study, versus just, the available evidence is limited. I mean, the first says something about the body of evidence is out there but warrants further study; then there's some reason to believe that the further study may illuminate some relationship.

DR. BELSITO: Or just the opposite and show that there's no relationship.

DR. SADRIEH: I think maybe it would be a good idea to kind of suggest what kinds of studies would be needed. Because, you know, the types of studies that have been looked at is case-control studies, which basically come with recall bias. So, I think that there's going to be inherently -- you're never going to find an association, even if you find a good relative risk or odds ratio, or whatever.

The question is, what would be enough? I guess, from my perspective, the way that this is being evaluated and by not really doing a systematic review, I don't know really what this kind of analysis is going to end up reporting; because there is no way of being able to get any information that is going to be useful in anyway.

I would maybe suggest that we look into the possibility of the types of studies that would be useful. And if they are prospective study that has to be done, then how would they have to be done? And if it's a systematic review of the existing literature, then how would that have to be done, to then weight the studies such that we actually can draw conclusions that are useful?

Because right now it's just kind of look at the information, you know, the previous data that wasn't conclusive. This date is not conclusive, I doubt that any data is ever going to be conclusive if we keep looking at the information in this manner. Thank you.

DR. BELSITO: Bart, maybe we can get back to Luigi and ask him what kind of studies he would, as an epidemiologist, believe would answer this type of question. And then further studies, further prospective studies, further da-da-da kind of studies, would be needed.

DR. HELDRETH: We can certainly pose that question to him.

DR. BERGFELD: Is that in the purview of this panel?

DR. BELSITO: I think it's in the purview of the panel to try and determine the safety of hair dyes. Normally, we don't conduct studies, but we're having an epidemiologist look at this and saying that the studies that exist aren't adequate.

And we will oftentimes, in the purview of the panel, say we wanted 28-day dermal toxicity and if it absorbs in other toxicological endpoints. So, we're not specifying the study in detail, but getting a comment as to what kinds of studies might help address this situation.

DR. BERGFELD: Most of the data, though, I believe said in 1980 there's a change in the epidemiology looking at breast cancer. The earlier dyes may have been carcinogenic. The newer dyes --

DR. BELSITO: The big issue is the new data that suggests African American woman have a higher risk of breast cancer with hair dyes; which sort of raised, for a lot of people I think, the question, are darker colored hair dyes of greater risk in terms of breast cancer? And that's always been a question in regard to other types of cancers as well. I do think that needs to be addressed in some fashion.

DR. BERGFELD: And also, they have to define what hair dyes they're actually using. Some of them are old types.

DR. LIEBLER: We talked about the conclusion and how the report just sort of stopped at the end of the narrative of the data review. Sometimes, when you have a document like this, it helps the reader to have not just a conclusion, which is usually very brief and probably maybe overly general, to have maybe a couple of paragraph discussion that summarizes the outstanding issues and what are the issues that probably won't be resolved by further studies of the types that have already been done and the meta-analyses that have been done.

So, in other words, what are the -- anyways, Don just pointed out, the association with breast cancer risk in African American women with hair dyes. That seems like a significant, interesting issue that could be resolved by another focus study, possibly. But the broader question of hair dye association, we've got actually a lot of data. And it's basically very modest affects and the data are consistently inconsistent. In other words, there's a consistent marginal affect a little bit. Plus, a little bit, you know, higher than 1, a little bit less than 1.

But I think perhaps a paragraph that summarizes kind of what are the main outstanding questions that remain, and what issues are probably not going to be resolved any better than they're currently resolved, followed by a conclusion.

DR. SADRIEH: That may be true, but at some point, one has to address how one would resolve

these questions. I think, you know, there has to be a way to be able to move sort of the answer a little bit forward, other than to say that, you know, there's no way that a link can be established because --

DR. LIEBLER: No, I wasn't saying that. I wasn't saying that. I think sometimes it's good to just step back and say, okay, what have we learned? What are the questions that we could resolve, and how could we resolve them? And what are the questions that we're unlikely to be able to resolve with these types of studies?

DR. SADRIEH: Right. But then we also have to say what kinds of studies would we have to do in order to -- so, identifying the deficiencies is one thing. But we have to also say, how are we going to address the deficiencies.

DR. HELDRETH: Isn't part of the answer to what kinds of studies would be done, it would be studies other than epidemiological studies, typical carcinogenicity endpoints that we would study where we were looking at a chemical and we're seeing an endpoint effect?

DR. EISENMANN: Hair dyes are very carefully studied for genotoxicity. And they've been coming up negative, the current hair dyes that are used.

DR. SADRIEH: Yeah, but you can't answer sort of the human risk aspect with the genotox or an animal carcinogenicity study. You have to look at human data. And I don't think you could do a human cancer study. So, you're going to have to look at epidemiology data and, you know, the studies have to be either prospectively designed -- I mean, I think a lot of the studies here are sort of other studies that were being done and they kind of asked an extra question about hair dye use, without knowing which hair dye, how often, what was the formulation, anything. So, you know, I think it's very difficult to draw conclusions from doing such a superficial review and then coming up with a conclusion that, you know, there's no evidence. Because I think that can be even more misleading than anything. Because you really haven't done the effort of trying to answer the question or identify what needs to get done to answer the question. And then the response is somewhat minimal and probably not helpful to the public.

DR. EISENMANN: One other comment that we have on our comments is back in 2006, Dr. Rollison did that paper and suggested the scoring of exposure for every epidemiology study. And that's been taken out of the table of this report. We'd like to see it put back in and, for the new studies, for that scoring to be added. So, it would be rated as to -- was the exposure just yes or no or was it more in detail about --

DR. BELSITO: So, you're talking about what is a Gemlish (phonetic) score? Is that what you're asking about?

DR. EISENMANN: No, it was Dr. Rollison score. It's in the text of some of it, and it used to be in the table, but it has been taken out. If they need the paper again, we can provide it. But she explained how to score exposure.

DR. ZHU: We have the paper, so I can add it back into the table.

DR. SADRIEH: Thank you.

DR. BELSITO: Any other comments on hair dye? Okay.

DR. BERGFELD: I have a comment. It would seem to me that this hair dye document needs to come back again for review comment.

MR. GREMILLION: Just kind of random observation. On Page 18 of the PDF, he says, "Taking skin cancer aside, breast cancer is the most common cancer diagnosed in women worldwide." And that's at odds with the World Cancer Research Fund International. They said lung cancer was the most common cancer; and skin cancer is down there, pretty far. There's just some odd --

DR. BERGFELD: Usually melanoma ranks about third or fourth.

DR. BELSITO: Yeah, but skin cancer is not just melanoma; it's basal cell and squamous, which aren't reported. So, he's correct. And this is speaking about women, not population in general. And I think it's men who skew lung cancer ahead of breast cancer. Any other comments? Okay. Polyaminopropyl Biguanide.

Day 1 of the June 4-5, 2018 Expert Panel Meeting – Dr. Marks Team

DR. MARKS: Oh, now we're into the hair dye epidemiology. That's going to be significant. Here we go, let's see. Where do I have that? Here it is. And I am not fluent; and I assume -- is this Chinese?

DR. ZHU: It's Jinqiu.

DR. MARKS: Jin --

DR. ZHU: Jinqiu.

DR. MARKS: Jinqiu.

DR. ANSELL: A new CIR writer.

DR. MARKS: Oh, I know that. I was getting the pronunciation of Jinqiu's first name. And the last name is Zhu?

DR. ZHU: Zhu.

DR. MARKS: Zhu. So, I could say Dr. Zhu. That actually is easier in some way. But at any rate, thanks for your memo dated May 23rd. We had the latest draft. Particularly, regarding breast cancer incidences and the evaluations from Dr. Naldi.

And one of my comments, I guess, I would make, right off the bat; and then I'll ask Ron, Ron and Tom, is Dr. Naldi -- if I recall correctly, he's the head of dermatology at Vicenza. Is that correct? University of Vicenza?

DR. ZHU: He's also an epidemiologist.

DR. MARKS: Yeah, okay. I figured that. Well, not figured, I assumed, that had to be, that he was being used as an expert in epidemiology. But probably some way that should be captured. Obviously, now it's captured in the minutes.

I expected that would be the case, but I was a little bit interested. A dermatologist, also an expert in epidemiology. Not excusive, obviously, but it's not very common in my experience.

DR. HELDRETH: Yeah. Dr. Belsito had recommended him because with his work in epidemiology, he's also helped the RIFM panel as well.

DR. MARKS: RIFM, okay. That makes sense. I didn't know that history. But at least now it's in the minutes. Comments on this? And then there was some -- was it this morning that we had -- yes, this morning we got a memo from Alexandra Kowcz. How do you pronounce her last name?

DR. HELDRETH: Kowcz. Yeah, Kowcz.

DR. MARKS: Codish. Huh?

DR. HELDRETH: Kowcz.

DR. MARKS: Kowcz.

DR. ANSELL: Like the company.

DR. MARKS: Okay.

DR. HILL: Put me in coach.

DR. MARKS: At any rate, there was some comments there dated June the 4TH, so we should note those. Key issues, additional considerations. First, do you want to make any comments, particularly, about -- Dr. Zhu, in reference to the comments from the industry liaison to Bart?

DR. ZHU: You mean my comment on the --

DR. MARKS: Yeah. Do you want to preface anything either --

DR. ZHU: Yeah, I agree.

DR. MARKS: Dr. Naldi and this memo here? You've had a little bit longer time to see it, not much, than we had.

DR. ZHU: Okay. I have the comment.

DR. MARKS: While you're looking at that --

DR. SHANK: Nothing to add.

DR. MARKS: Ron Shank, nothing to add, okay. You like it.

DR. SHANK: Yes.

DR. MARKS: Okay.

DR. SHANK: Very clear.

DR. MARKS: Tom?

DR. SLAGA: Same here. I didn't have no problem with it. Very clear.

DR. MARKS: Good. Okay. Did you look at the memo?

DR. SLAGA: I left mine in the other room, I think.

DR. MARKS: We'll take a minute and let -- Tom, for you to look at the memo. And I see that both Rons are reading over the memo also.

DR. WYATT: Is there an extra copy of the memo from Alexandra?

DR. MARKS: Pardon?

DR. WYATT: Is there an extra copy of the memo from Alexandra?

DR. MARKS: I just gave mine. A minute ago, I would have said, yes. But -- do you have an extra copy of the memo?

DR. ZHU: Yes. I have it.

DR. MARKS: Could you give me a copy or give this gentleman a copy.

DR. ZHU: A copy? I just have it on the computer.

DR. WYATT: My name is Mr. Wyatt; I'm with the FDA.

DR. MARKS: Okay.

DR. HILL: Should I go check out with Carla and see if there's one out there? An extra? There usually --

DR. MARKS: Well, if you've read it, maybe you could loan it.

DR. HILL: He's got an electronic, doesn't he? I thought that's what he was saying.

DR. HELDRETH: We don't have any extras. We got these this morning too.

DR. MARKS: Oh, you got it this morning too. Okay, so that is real time.

DR. WYATT: Understood, thank you.

DR. MARKS: Would Carla have it? Carla wouldn't have extras. I gave mine to Tom.

DR. ANSELL: Okay, we have one.

DR. MARKS: Do you want to look through it? Did you get to skim it or not?

DR. WYATT: I can just --

MS. FIUME: I know it. Yeah.

DR. MARKS: You know it.

DR. WYATT: I could just do the cursory look.

DR. HILL: Because it's not on the website yet, right? You got a phone, you could take a picture of it.

DR. MARKS: Again, Dr. Zhu was -- did you get to read the memo?

DR. ZHU: Yes.

DR. MARKS: Is there any comments the way you're going to change the boilerplate? I guess it's -- I'm not sure. I guess the boilerplate or at least an epidemiology update. Was there anything in the memo that you specifically --

DR. ZHU: The comment on the paper 2017, Dianatinasab paper; so, this comment indicated that the word, you know, risk should not be used. Instead use the association. Actually, the risk word, this word, risk, is used by the author in the paper. So, I just quote that.

But actually, I agree that we can use the word association instead of risk. Because, you know, in this paper there are multiple disparate factors has been compared. I think the -- because some of them shows a positive result; some of them shows a negative result. In our document, I agree that we use association instead of risk.

And I agree, you know, in the Table 1, we should correct that -- that should be prostate cancer instead of breast cancer. And also, I agree that in Dr. Naldi's write-up of the 2015 paper, because this here it indicated that when the odds ratio for more than 19 hair dye episodes used, that information has not been included in our Table 1. We should include that into our Table 1. Yeah.

And also, the comment on Dr. Naldi's write-up of the Mendelsohm 2019 paper; yes, I think Dr. Naldi just did not say clearly here, that -- but that should be corrected in our revised version about the three years use of the hair dye survey; that information can be updated. And several other things, you

know --

DR. MARKS: Okay. Tom, any comments? You still like any -- and these changes suggested in the memo, they're fine?

DR. SHANK: Yeah. The editorial changes.

DR. SLAGA: Minor, yeah.

DR. MARKS: Yeah, they're fine. I think the bottom line is when I read -- and that's not yellow, but I want to be sure, Tom, Ron and Ron, you're fine with this. The conclusion is, the CIR expert panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer, based on the lack of strength of the associations and inconsistencies of the findings.

In addition, the panel noted there was no consistent pattern of genotype/phenotype influences on hair dye, epidemiology findings. These new studies all support, still, that conclusion.

DR. SLAGA: Yeah.

DR. MARKS: Okay. Because that's the bottom line for this. Okay, any other comments?

DR. SHANK: I don't see how they'll ever show an association between something like hair dye use and adverse health effect.

DR. SLAGA: Yeah, even if it's a specific --

DR. SHANK: You have to do individual -- they're not all the same.

DR. MARKS: Right.

DR. SHANK: And until you do a quantitative study, on particular dyes, you really have a very slim chance of coming up with a significant association. Not that there is or isn't one, it's just there's no power to the analysis.

DR. HELDRETH: I think that's probably what the casual reader wouldn't conclude. They would wonder, okay here's all these studies and we don't think it's a problem. But I think the explanation you just gave would be a great addition, I think, to the document. I think that would make it clearer.

But it's up to you whether or not we should make that kind of addition. Because I think there's a couple instances, throughout the document, where it says further study may be warranted. But as you mentioned, the study's probably not possible.

DR. SHANK: Right.

DR. SLAGA: You'd never have enough with one specific hair dye.

DR. SHANK: Would you be willing to put that kind of statement in the hair dye epidemiology -- what do we call this -- paper? It's up to us?

DR. HELDRETH: It's up to you.

DR. MARKS: Document. That's what the -- Jinqiu? Am I saying that correct?

DR. ZHU: Yes.

DR. MARKS: Jinqiu, that's what he has. Hair dye epidemiology document. So, it's a document.

DR. SHANK: Document.

DR. MARKS: So, it's already now in the minutes for public consumption. It's not a matter of -- the question is, do you think it should be explicitly put in this document? That's very interesting. And would that help guide future epidemiologists in terms of trying to really determine.

DR. SHANK: Well, doing more studies like this, even with genetic markers -- there's one that had interesting genetic markers -- is not going to give you the scientific power to identify which dye.

It's not hair dye use that's going to cause cancer; it's particular hair dye that could. And if you lump them all together, with no quantitation or very little quantitation --

DR. SLAGA: Well, you have the delusion effect of bringing them all together, too.

DR. ANSELL: I don't think we are directing research. I think -- and Linda's clearly the expert here, but I think our process has been to continue to monitor the research and to make it available to you guys. I think your point's well taken, but none of us are actually running a research program.

I don't know how we would even -- what we would do, just send it into the ether, saying we

think this would be type of study --

DR. SHANK: We can dictate studies. Every time I read further studies are recommended, I kind of cringe. Because these are extremely expensive studies. Epidemiology is not cheap.

And if you start off, really, with a very poor chance of coming up with a meaningful association, it's money not well spent. But I don't think we can say that in our document.

DR. SLAGA: We can't dictate that.

DR. ANSELL: Nor would you suggest that we stop our monitoring and reporting?

DR. SLAGA: No. No.

DR. SHANK: We should continue to monitor; I did not mean that. But I don't like recommending more studies.

DR. ANSELL: Okay.

DR. MARKS: And I think that's an important point. Because if we recommend more studies, then we should give what we think the studies may be. If I understood what you said, Ron Shank, correctly. If we're going to identify any cancer potential, it needs to be for specific dyes, not in a general --

DR. ANSELL: But we don't say that, do we, in our summaries; that we recommend additional studies?

MS. LORETZ: Oh, no. No.

DR. ANSELL: Our roll, or what we've taken on as our responsibility, is to continually monitor the research as it's being done with all of its bumps and bruises. And just make the panel aware that -- I think there was a specific study, which Don wanted to have an expect look at, and he's provided his comments.

DR. SLAGA: Yeah. I mean, no and that's important in itself.

MS. LORETZ: So, this gets revised then? I mean, and then what happens next? Or is there another comment period? Or how does that work?

DR. HELDRETH: If there's going to be substantive changes to it. If it's something as simple as changing the verbiage or put the relevant study back in the table, where it was before, and nothing's really changing and the conclusion's not changing, the panel can say go ahead with those changes and it's fine. But if you want to add some verbiage that's a substantive change, then, sure, we would want to put it out there for public comment again.

DR. MARKS: I think, addressing Ron, we do say if we use this document as such. If you look on page 9, just as Ron said, it's in the yellow highlighting right above genetic polymorphism.

The last sentence. "While these findings do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted." And that's exactly what Ron is talking about.

I think, Ron, the question is, do we want to keep that sentence or eliminate that one. Because that's exactly what you were talking about.

DR. SHANK: It's almost the standard statement, more research is needed. Every scientist says that because --

DR. MARKS: That's how they keep busy.

DR. SLAGA: That's how you get money.

DR. SHANK: I had to stop midsentence on that.

DR. MARKS: Yeah, I know. But I'll finish it.

DR. SLAGA: I don't want Ron on my review committee if I submit an epidemiological study on hair dyes.

DR. HILL: Well, but it is a policy question, and this is something off -- it's on the record, but it's off the record. Is do you spend a lot of money on an epidemiology study; or is it better to go at it from the other direction. Okay, we have this mechanism, is there any connection to a dye that's being used, potentially.

You know, and to me, you spend the money on the biology, in general, keep the epidemiology cooking maybe; but the only one that I ever saw even a whiff was for about 10,000 professional hair

dressers in China. And there wasn't still not statistical power, but a whiff of something that makes some sense. And that was the best I've seen in all of it.

DR. MARKS: So again, just to continue beating this horse, on Page 5, right above lymphoma and leukemia, again, while Tai et al. findings are limited and do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted.

We're back with ending a lot of these by saying, well it didn't show anything, but do more investigations. I shouldn't say it didn't show anything, it didn't support a causal relationship. Do we want to just eliminate those parts of this document that says further investigation? We know they're going to be further investigation.

DR. SLAGA: It's followed by maybe, so it's okay.

DR. MARKS: Yeah, maybe.

DR. SHANK: It doesn't say epidemiological investigations. But keep looking for --

DR. MARKS: Further investigations. Yeah, that's true.

DR. SHANK: Keep looking for any risk.

DR. MARKS: Okay. No, I think --

DR. ANSELL: I also think there's a difference between reporting that the author has concluded versus the panel recommends.

DR. MARKS: Right.

DR. ANSELL: And so, this is, well his finding are limited, so who is saying additional data here?

DR. HELDRETH: We are. That was the verbiage -- we were following up with what Dr. Naldi was saying. And so, we characterized it in the way that he had. And he makes those kinds of statements throughout, further should be done.

DR. ANSELL: So, I think we could change that.

DR. MARKS: Well, I don't know that we need to change it, because I think Ron's comment that when you say further investigation, that leave it wide open, not necessarily epidemiologic investigation.

DR. SHANK: That's right.

DR. MARKS: I think I like the way you interpret that. I think leaving it in, from my mind is fine. If that's okay with Ron, Tom and Ron.

DR. SHANK: It is with me.

DR. HILL: It is me, too; because I think investigation means if there really is -- I mean, you make the hypothesis there really is something and then try to figure out if there's mechanism. And of all the things society spends money on, to me, science should be more and other things less. There's never enough science.

DR. MARKS: Okay. We're going to be seconding, probably, I would think, a proposal to post this revised draft hair dye epidemiology document on the website. And we like the way it is, and our minutes will capture the nuances about doing epidemiologic studies on specific dyes, not general dye exposure. And that further investigations covers the waterfront.

DR. HILL: We did see something interesting from a presenter -- not the last meeting, but I think the meeting before -- that looked at differences between light colored hair dyes, certain exposures, versus dark ones. I thought that was an example of, that's interesting now let's see what that means.

DR. MARKS: Okay. Any further comments? Thank you Jinqiu. The J is like a Z? Jinqiu.

DR. ZHU: Yes.

DR. MARKS: Good. You're going to educate me. I apologize for my ignorance.

DR. HELDRETH: He's also told us in house that we can call him James. So, if that's easier.

DR. MARKS: James.

DR. SLAGA: What was that? I didn't hear.

DR. HELDRETH: Oh, he also told us in house, instead, we can just call him James if we want to.

DR. SLAGA: James?

DR. HELDRETH: Yes.

DR. MARKS: I may revert to that in the next meeting if I can't remember. I mean it's just knowing how to -- the J is a Z. Jinqiu.

DR. ZHU: Jinqiu.

DR. MARKS: Jinqiu. Okay. Thank you for tolerating us. Okay, we've got a little less than 15 minutes to go to lunch. We can do the next one. This is straight forward, right?

DR. SHANK: Sure.

DR. MARKS: Yeah, sure is right. Well, it's only one ingredient, correct?

DR. SHANK: Yeah.

Day 2 of the June 4-5, 2018 Expert Panel Meeting – Full Panel

DR. BELSITO: First of all, we liked the council's suggestion that these boilerplates be referred to as resource documents, going into the future; we like that terminology. In terms of the hair dye resources document, Dr. Naldi did some analysis, particularly on the new information that had come in regarding associations between hair dye use and breast cancer, particularly in African American women, and we appreciate that very much.

There were two additional studies that were available, subsequent to his analysis, that we would request that he relook at. And there was also concern, particularly from the Consumer Federation of America, with his last sentence that says, "While these findings do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted." And, therefore, I think a request should go back to Dr. Naldi as to clarifying that statement and what kind of investigations would be needed to try and resolve this question.

DR. BERGFELD: I'm sorry to interject, but being in your team meeting yesterday, was there also a suggestion of reformatting this document?

DR. BELSITO: Yes, that has to do with reformatting; the fact that the conclusion is stated up front rather than at the end and having -- we agreed that there can be discussion at each endpoint in terms of the cancers looked at, as to our assessment of the data that has been presented in terms of whether there is risk or not. But then at the end of the document there should be a final conclusion rendered, rather than the conclusion up front.

DR. BERGFELD: Thank you. Any comments. Dr. Marks?

DR. MARKS: Yeah, Ron Shank, I think had a pithy comment yesterday. Rather than me try and paraphrase it, Ron was referring to the epidemiologic studies as I understand. And as long as they're done with multiple dye exposures, it's hard to come to a conclusion. That really needs to be with a specific dye.

And that, actually, we thought that further investigations was not a bad -- maybe clarify it -- but how we interpreted that is it covers all science and all toxicity. So, as we get more mechanistically driven, those would be the studies that probably would help us move forward. But Ron, please clarify what I think I heard you say.

DR. SHANK: You said it right. I think when you do epidemiological studies, such as been done in the past, where you're having a very broad sweep of the cost of agent, hair dyes, that's way to general to give any power to the epidemiological study, to come up with an association. And future studies should focus on particular hair dye. And there're many of them so this is probably going to be very difficult to achieve. So, when we say more studies should be done, I think what we mean, more studies but not just epidemiological studies.

Basically, that was it; that I thought the CIR panel should continue to monitor new information that comes out. But I don't think we should say there should more epidemiological studies, in particular, more investigations.

DR. SNYDER: Can we use language along the effect that these are largely observations, and that the cause and effect remains to be determined? Something along that line, rather than specify studies. We just say that the cause and effect remains to be determined.

DR. SHANK: Yes. Thank you.

DR. BERGFELD: There was some suggestion yesterday that we -- in the formatting of this particular resource document and perhaps the innovation one as well, in some other white hat kinds of statements that we've made -- that we put them together similar to how we put our ingredients reports together. With an abstract, what's been considered, and then the fill-in parts, as well as then a discussion and a conclusion. And I think that would be a better reading document.

Because this one left me particularly cold; what else is new kind of thing. All right. Well I think that we'll move forward with that. We don't need to have any vote on that, do we?

DR. HELDRETH: I don't believe so.

DR. BERGFELD: No, I don't think so.

DR. HELDRETH: Going forward Jinqiu will go through and make these sorts of edits, and reformat the document, and then it will come back to the panel again for finalization.

DR. BERGFELD: I think that you were going to also contact Dr. Naldi, and request what from him?

DR. HELDRETH: From Dr. Neldi we'll be requesting his outlook on what is meant by further investigations; and to have him look at the two studies that were discovered after he did his analysis.

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MS. FIUME: Okay, so the next two require Jinqiu's input because he prepared these two admin documents. So I'm going to go over and see if he is available if that's okay.

DR. MARKS: Sure. Yeah, I agree with you. Hair dye epi and then the aerosols and inhalation are the last two I have. And they're both in the admin section. And then we got, in Wave 3, the letter from the Women's Voices for the aerosols.

DR. ANSELL: That's an interesting reading.

DR. MARKS: And I don't think we got anything on any hair dye in the supplement.

DR. SLAGA: I didn't see anything.

DR. MARKS: Pardon?

DR. SLAGA: I didn't see anything either.

DR. MARKS: Yeah, okay. Let's go in the Admin Tab, and hair epidemiology. Okay, so let's go ahead to the revised draft, hair dye epidemiology document. There's a memo from Jinqiu, data November the 9th, in which he incorporated Dr. Naldi's comment, and they are highlighted in the text. That's Page 59. So, the memo is Page 30. Fifty-nine is the memo under the discussion. A lot of it's highlighted in yellow. Did we get anything more about the hair dye this morning?

MS. FIUME: Yes.

DR. MARKS: I thought there was another document. I don't know what I did with that. Thank you. Tom and Ron and Ron, did you see this? One of the issues the council had is description of "ideal epidemiologic study" in the discussion. And then talks about the discussion is not appropriate because it focuses only on breast cancer. A more general discussion of the epidemiology would be helpful. Did you see this, Tom? Were you able to read this?

DR. SLAGA: I'm looking for it right now. Yeah, I got it.

DR. MARKS: Good. Should we take a minute? Were you able to read it this morning?

DR. SLAGA: No. I didn't.

DR. MARKS: Okay. Well, then why don't we take a minute, because I don't think we can make recommendations without considering this memo.

DR. SHANK: I left them in the other room. That's why I don't have it here.

DR. MARKS: Yeah, okay. And I'll be giving you the next one on the aerosols. Why don't I give you that right now. Because this will be our next one after this.

DR. SHANK: Thank you.

DR. MARKS: You're welcome. Tom, you read it? Ron Hill, you're close?

DR. HILL: I'm essentially at the end.

DR. MARKS: Okay. So, we're on Page 59 in the Admin folder. And the first paragraph talks about linking hair dye use and breast cancer. And the council didn't feel that that focus, perhaps, was appropriate.

DR. SLAGA: I agree. It's too much focused on breast cancer.

DR. MARKS: How would you want to change that for Jinqiu? Obviously, we're going to see another draft of this. This is really important, obviously. Unless it will be a simple --

DR. SLAGA: Their comments are very good about adding, to the discussion, the aspect of the meta studies and all that. It should cover everything the document lays out. The discussion should revolve around that.

DR. MARKS: So are you, Tom, talking about -- again, are we still on the first paragraph in terms of the council suggests that it should be a more general discussion?

DR. SLAGA: Well, it includes everything. All the cancers, some pros and cons about all the cancers, not just breast cancer. They bring out about the meta-analysis and how that should be discussed.

DR. MARKS: So, you would follow the council's recommendations for edits?

DR. SLAGA: Right. Or the committee on hair dye -- the technical committee on hair dye.

DR. MARKS: Okay.

DR. HILL: Can I ask about their first paragraph? Again, I appreciate the fact that if new dye were to come along and it showed mutagenicity, it would be rejected at hand. But we do have legacy dyes that are out there under the Coal Tar exemption that are strongly suspected carcinogens if not known carcinogens.

I mean, over time I'd expect those to disappear because of the increased restrictions of the European market and that people don't like to just market in the US. But it's not accurate to say that we have no hair dyes on the market that are not known carcinogens. That's not correct.

DR. MARKS: Tom, your response?

DR. HILL: I mean, I'm just responding to their commentary as to how you'd interpret that first paragraph in the document that's being finalized.

DR. MARKS: Well, I don't think it's going to be finalized with this rendition. Because the council's suggestions from the hair coloring technical committee are significant. I think we'll need to, Jinqiu, see the next addition. We'll see what the Belsito team feels. But basically, Tom, you would agree take this as the format?

DR. SLAGA: Yeah. No. They have some very good points.

DR. MARKS: Both as far as the focus on breast cancer, it's sort of flipped around. And then the description of the ideal epidemiologic study, "Shows a fundamental misunderstanding around hair dye safety. Individual hair dyes are assessed for mutagenicity and potential carcinogenicity as part of their safety review. And a mutagenic hair dye would not be considered acceptable for use." This is what you're talking about.

DR. HILL: That's what I'm talking about.

DR. SHANK: It has been in the past.

DR. MARKS: Pardon?

DR. SHANK: We have reviewed hair dyes that have been mutagenic, and said that they could be used safely as a hair dye because of the rinse off, low exposure. Do we really want to get into the position of recommending specific parameters for epidemiologic studies?

DR. HILL: I don't think so.

DR. SLAGA: I don't think so either. I don't think that's our charge. I don't think we have the expertise to do that.

DR. ANSELL: It really wasn't the question that we thought we asked either. Did we feel that we had all these epi studies and we wanted someone who could kind of wrap the whole thing up for us?

DR. SHANK: Yes.

DR. ANSELL: And not propose what an ideal study would look like. You know, including a study of 356,590 women. So, I think we certainly agree with this.

DR. SHANK: Okay.

DR. ANSELL: Not in this framework document.

DR. SHANK: I don't think we should go there.

DR. HILL: I have interpreted his commentary to suggest that -- really as suggestions of, here's the problem with the existing studies and were one to construct an ideal study, this is what it would have to look like. But not necessarily that he was making a recommendation that we should say this is what needs to be done.

We did discuss, at least informally at that meeting as I recall, what would you have to do to get epidemiology to mean anything whatsoever. Which is where I made the comment, the only time I've seen even a reasonable whiff was in the occupational study in Chinese hairdressers, where there was a large population. And even there, there was not statistical power enough to detect it. And that was some 10,000 people if I remember right.

I think our whole take on that was, we aren't going to get any firm answer from epidemiology which is definitely nicely written in here. We have to keep paying attention to it for obvious reasons. Everything else in here, though, I agree with. This is a great analysis.

DR. SHANK: If you can't quantitate exposure, you're dead in the water. Sorry, but that's just the case. And you can say dark hair dyes, never used, once in a while used, all this stuff. It's going to get you nowhere. You just don't know what the exposure is.

DR. HILL: My feeling about this sort of thing is the same as my feeling about computer modeling. It's a reasonable hypothesis generator that you get, then used to turn around and say, how do we study this mechanistically? The difficulty there is that analysts are humans. As we improve our abilities to do cell-based studies and try to interpret those, and translate those, we could at least do better and better mechanistic studies. Which in some cases we'll say, no there can't possibly be a connection. Best we can tell within the limits of science.

DR. SHANK: You can't say that.

DR. HILL: No, you never can.

DR. SHANK: That there can't be --

DR. HILL: I didn't state that the way I intended it, but --

DR. MARKS: So, with that in mind, on Page 59, the paragraph which states this is an ideal -- we're suggesting what the ideal epidemiologic study is, you would delete that whole paragraph?

DR. SHANK: Well, I would. Certainly don't call it "the ideal."

DR. SLAGA: Yeah. Nothing's ideal.

DR. MARKS: I hear that. I mean, we could --

DR. SHANK: I would leave it out entirely. I don't think --

DR. MARKS: Yeah. Because it gets back to your point of are we the one recommending what the study should be.

DR. SHANK: Right.

DR. MARKS: Now we could certainly have, in a discussion, about your point, Ron Shank, of a quantitative exposure has got to be crucial. I don't know if we want to --

DR. SHANK: Yeah. I mean, it's half of the equation.

DR. ANSELL: Or the difficulties of doing epi in this arena. But I think the document is intended to be kind of an overview. This was more of a letter -- or a proposal, as opposed to contributing to an overall assessment of hair dyes that we continually work on.

DR. SHANK: I think the way it started out, originally, is this is a summary of the data of epidemiological studies. We have 42 or 57 or 900, these are all of the studies that have been done, a compilation. And the end result is, there is no clear established relationship between hair dye use and cancer in the human population. And if you want to say, yet.

DR. ANSELL: And that's where we struggle, is how this yellow -- the added text contributes anything to that discussion.

DR. SHANK: I think it should just be, this is a boilerplate not a whitepaper on hair epidemiology.

DR. MARKS: Yeah. And as I recall, Ron, exactly what you said. And, periodically, we would update, it with these newer studies, to indicate that the panel had looked at the studies.

DR. SHANK: Right.

DR. MARKS: And evaluated them. So, this whole -- on Page 59 where the council made -- and, Tom, you agree that it should be broader than breast cancer. I'm trying to think, then what would we have under the discussion, just that?

DR. HILL: How about the first two paragraphs with some modifications of the second one.

DR. MARKS: I mean, ultimately the -- let me see. Let me go back here, 59. But it's constructed that we had the discussion, but the point -- and you have, Jinqiu, all these studies you mention ahead, but isn't right in the beginning. Then you go over the various cancers in the boilerplate, prostate, leukemia. The study summary. That was where it was continuously being updated with the new studies. And then background. We don't have a conclusion, do we?

DR. SHANK: No. Well, the conclusion is --

DR. ZHU: Page 60.

DR. ANSELL: Is unchanged.

DR. MARKS: Yeah. The conclusion is on Page 60. The panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

DR. SHANK: Right.

DR. SLAGA: Right.

DR. MARKS: The associations and other findings are lacking in strength and consistency. In addition, the panel noted there was no consistent pattern of genotype/phenotype influence on hair dye epidemiology findings. That's the conclusion as we have it.

DR. SHANK: Okay, the first half of it is fine. Where is that?

DR. MARKS: Page 60. Right at the top.

DR. SHANK: The conclusion?

DR. MARKS: Yes. I don't know that the last sentence is necessary.

DR. MARKS: Yeah.

DR. HILL: My interpretation of its presence there is just that that was not considered in the previous iteration of this document. And that it was looked at, but maybe that's not the right place to put it.

DR. ANSELL: Right.

DR. HILL: And if you figure out what actually should go in the discussion, maybe that would be in there.

DR. SLAGA: We could just leave that last sentence out. The first sentence is really the important one.

DR. SHANK: Yes.

DR. ANSELL: Yeah.

DR. SLAGA: It summarizes all of the studies.

DR. SHANK: Sorry. I mean, all that work -- a very nice analysis prepared. But for a boilerplate, I think, it's not necessary. And if you want to write a position paper or whitepaper, whatever you want to call it, as a statement of the panel, or a statement of the CIR, or a statement of the council, that's a different document. And then you can get involved in all the different parameters that effect exposure and effect --

MS. FIUME: So, Jinqiu, to clarify, the discussion is for the precedence document that goes on the website. This isn't discussion language in the report document itself, is it? It's is the discussion of the precedence paper? Is that correct? And the report will just refer people to the precedence paper?

DR. ZHU: Yeah.

MS. FIUME: Yeah. So that discussion language isn't being proposed for inclusion in the report itself; it's the discussion that goes with this whole precedence document.

DR. MARKS: Oh yeah, we understand that.

MS. FIUME: Oh, okay. I just wanted to make sure, okay.

DR. SHANK: That being the case, then you need to expand it in great detail.

DR. ANSELL: Or delete it all, because it doesn't have anything to do with precedence either.

DR. MARKS: Yeah. So, that was my next question is, do we even need a discussion? Because we're updating every -- with the studies. Now, Jinqiu, all the discussion on the studies, preceding the discussion, they are repeated in the table below, correct?

DR. ZHU: Yeah.

DR. MARKS: Yeah. Okay. So, what you do in the text portion of it, you're just expanding the table. I mean, none of the questions would be --

DR. ZHU: Yeah.

DR. MARKS: Do you need -- again as, I guess, a position paper -- do you need more than the conclusion and the table in the references?

DR. SHANK: I think we're talking about two very different things.

DR. MARKS: A boilerplate, I'm sorry.

DR. SHANK: The table is great.

DR. MARKS: Yeah. I agree. What I'm wondering is -- the table's redundant to what's in the text prior to the discussion, do we really need the text?

DR. ANSELL: In this, I think, the background, on PDF 53, the following provides a brief summary of what's come out since the last time we did this.

DR. MARKS: Right.

DR. ANSELL: And then to the extent that it doesn't change any of your conclusions --

DR. MARKS: So, you're fine leaving the text in and then having the table, which is a summary of it.

DR. SLAGA: Yeah.

DR. MARKS: Okay.

DR. ANSELL: Striking all of the --

DR. MARKS: Discussion?

DR. ANSELL: Yeah.

DR. HILL: What don't you like about the first two paragraphs of the proposed discussion, which kind of recaps and distills concisely?

DR. SHANK: To narrow.

DR. HILL: To narrow?

DR. SHANK: Yes.

DR. MARKS: Yeah. It starts right off the bat by saying -- linking hair dye use and breast cancer is limited. I mean, it's really between hair dye use and cancer, period.

DR. SLAGA: Right, period.

DR. HILL: So what if you take out that first sentence and start reading from two systematic reviews, three case-control studies and one cohort study?

DR. ANSELL: Because there's more than that.

DR. MARKS: "All published since 2004 were evaluated for --"

DR. ANSELL: Yeah. I mean, then you leave out anything that isn't involved with the breast. That statement is specific to breast cancer.

DR. SHANK: What we've done is just review all of the studies that are out there, published mostly. That's it. And we can't conclude a cause and effect relationship. All of this other stuff is unnecessary.

DR. MARKS: Yeah. So it would be a very short discussion.

DR. ANSELL: Yeah. Because the purpose, as stated in the introduction, is we did this last in 2010, and here's what's been published since that time. And looking at bladder and prostate and leukemia --

DR. SLAGA: Lymphomas.

DR. ANSELL: Lipomas, breast cancers. And then we determined that the available evidence

do not provide sufficient evidence for causal relationship. I think that's a --

DR. SHANK: That's where I'd go.

DR. MARKS: Which is essentially what we say in the conclusion.

DR. SHANK: Yes.

DR. MARKS: Do we need a discussion?

DR. SHANK: No.

DR. MARKS: Is it important, all the references we have there's not, Jinqiu -- the reference to the external expert, in the epidemiology field, is that important to capture? Because that wouldn't be in the table, is it?

DR. SHANK: That would not be in the table.

DR. ANSELL: Because he didn't actually do one.

DR. MARKS: No. So, I mean, is it important to reference that we had an external, or that will just appear in the minutes of our meetings. And that we did look at Naldi's review. Again, I only raise this because this will be the boilerplate, which now will be in place for probably another decade. And is it important to capture that we --

DR. ANSELL: But he didn't do --

DR. MARKS: No. He didn't do any of these, he just reviewed things.

DR. ANSELL: Well, he's proposing what an ideal study for breast cancer might look like.

DR. MARKS: Oh yeah. Exactly. Which we're deleting.

DR. ANSELL: But what we wanted him to do, I think, was to take a look at all the new stuff, as an epi expert, and see whether it changed our 2010 conclusion.

DR. MARKS: Right.

DR. ANSELL: And what he did, was come back and said well, no; but if we wanted to know a real answer, here's what he would propose.

DR. MARKS: Yes.

DR. ANSELL: So, I don't see it contributing to this. I don't think we should lose it. If anyone wants to fund the 400,000 women study, I'm sure he'd be happy to --

DR. SHANK: For each hair dye?

DR. ANSELL: And only breast cancer.

DR. SHANK: And only breast cancer?

DR. ANSELL: Yeah. So, we'll have one ready.

DR. MARKS: So, my sense is we just delete the entire discussion; and that addresses the issues that the council brought up?

DR. SHANK: That's where I'd go. In the beginning we say how we reviewed all these studies, summarized in table one.

DR. ANSELL: Yeah. You could add to the conclusion that we reviewed all the studies above.

DR. MARKS: Yeah, I'm not sure it's worth it, because the conclusion covers that.

DR. ANSELL: Yeah.

DR. SHANK: Yeah.

DR. MARKS: We'll see how it goes tomorrow, but I'm going to put delete discussion.

DR. SHANK: Maybe I'll have to leave early.

DR. MARKS: Well, no. It'll be done in a professional way. And we'll see what the Belsito team feels. I mean, they may want to expand. Delete discussion. Okay.

DR. SHANK: Great.

DR. MARKS: That addresses the issue of broader than breast cancer. And it addresses, also, the ideal study issue. And we'll see.

DR. SLAGA: Sounds good.

DR. MARKS: Any other comments? Thanks.

DR. HILL: I'm actually shutting my mouth and rereading all of this, so that I knew exactly what it said. I now concur.

DR. MARKS: Okay. Next is the aerosols and inhalation. And I'll be recommending that and

I think that's our last one. So, with that in mind if we just delete the discussion, we're at the final boilerplate. Because there's no need to reread. Other than we're going to delete the discussion, we're modifying the conclusion. Because we're deleting that sentence in the conclusion, Ron Shank, you had asked.

DR. SHANK: When did we start using precedent documents? After?

MS. FIUME: A while.

DR. SHANK: Really?

MS. FIUME: They're on our website that way.

DR. SHANK: As precedent documents?

MS. FIUME: Because the term boilerplate and framework didn't fit; because it's not a boilerplate, it's a resource document, actually, is what it's called.

DR. SHANK: Yes.

MS. FIUME: It's a resource document. And so, the discussion refers to the resource document link. Where everyone can go and see why we say what we say about hair dyes, or inhalation information.

DR. SHANK: Okay. And now that's called a precedent?

MS. FIUME: Resource document.

DR. SHANK: Resource?

MS. FIUME: Yes. It's probably been at least four to five years.

DR. SHANK: I'm a slow learner. Okay.

DR. ANSELL: Well, this is significantly different than the resource document for pesticides and natural products. So, I could see why this would not pop out, instantly, as the type of thing we've been doing for a long time.

DR. HILL: Well, in part because we review a hair dye once a year. All though, of course, I don't come to a couple meetings.

DR. MARKS: Okay. So, for the hair dye epidemiology, I'm going to propose, tomorrow, after the Belsito team has commented, that indeed we did take into consideration the technical committee's recommendations for editing the discussion. And we felt the best way to edit the discussion is to delete it. And then we also wanted to delete a sentence in the conclusion on Page 60, and I'll read that. That's the second one, second sentence. So, I'll read that tomorrow. That's Page 60. Okay.

That was an interesting -- and then the resource document, we have a history of that, but I won't repeat that. I think it is different with the hair epidemiology, because there's so much epidemiology studies that come out. Hot topic, so to speak, so in contrast -- to some of the other. That's why I think it's updated. And I like the way -- the table, I think, it's very good in summarizing it. Go ahead, Ron Hill.

DR. HILL: You said the second sentence, but there are three sentences.

DR. MARKS: Oh, are there? I'm sorry.

DR. HILL: The one with the no consistent pattern of genotype/phenotype influence.

DR. SLAGA: Yeah.

DR. HILL: Is that the one that we're taking out?

DR. MARKS: Yes.

DR. HILL: Okay.

DR. MARKS: The last two sentences. I'm sorry, you're right. We weren't going to do, "The association and other findings are lacking in strength and consistency." Were we going to delete that? And just leave the first sentence, "The CIR expert panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer." And that's it. Yeah, thanks for clarifying it. It's the last two sentences.

DR. HILL: Because tomorrow you'll be going fast and --

DR. MARKS: I won't be going fast. I would hope tomorrow you would say the same thing.

DR. HILL: You'll be reading your notes and then create confusion.

DR. MARKS: Yeah, you got that right. I will definitely be reading my notes. Delete two sentences.

MS. FIUME: And can I just clarify. I think someone had said those were new sentences. At least that last sentence. That's been there since 2014.

DR. HILL: The genotype/phenotype was in there?

MS. FIUME: Yes.

DR. HILL: Okay, it's not new.

MS. FIUME: Just so you know, it's not a new sentence.

DR. HILL: That was me. Okay.

DR. MARKS: Okay, thanks. That's what we'll recommend tomorrow. I like it cleaner with just the one sentence. Okay, any other comments? If not we'll move on to the aerosols and inhalation.

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DR. BELSITO: So, hair dye epidemiology is next. That's in the admin book. And then we got another handout this morning, is that correct?

DR. LIEBLER: It starts on page 30. It's the memo.

DR. BELSITO: I thought it was good. I really didn't have any comments. It looks like the council had some. Description of the ideal epidemiologic study in discussion section includes recording use concentration of all -- I did not have any comments, the council had some. And maybe you want to comment on your comments, rather than my reading them?

DR. BERGFELD: Well, there's a lot of them.

DR. EISENMANN: The comments are coming from the Hair Coloring Technical Committee. They reviewed it. And they're a little concerned about Dr. Naldi's comment, that before doing the epidemiology you should look at what components are carcinogenic and mutagenic. The industry does not put carcinogenic or mutagenic hair dyes into hair dyes.

There was an agreement, way back in 2003, in Europe to do a certain standard set of mutagenicity studies on hair dyes, which are being done now. And US hair dyes are very similar to what are used in the European market.

The other concern is with the discussion. It's more or less the discussion focuses just on breast cancer, and we don't think that that should be the focus. In general, for epidemiology studies, fairly common exposures and fairly common cancers will come up with an association. Another evidence is that you have a positive prostate cancer study, and you don't mention that at all either, in the discussion.

We want to be clear that epidemiology is one tool, and that you also have to look at the genotoxicity potential of the hair dyes and exposure. And whether or not the study suggested, by Dr. Naldi, should even be mentioned, is also a concern because it's such a large -- yes, and nice power calculation on how many people you would need to show an association, but it's pretty unrealistic. No one is ever going to do such a large study like that.

And then if you leave it in the document -- I'm not sure if it came through an email, or how you go the information from Dr. Naldi, but I didn't see it other than cited in the report. So, everything needs to be publically available. So, the email has to be put out somewhere publicly rather than just to cite.

DR. ZHU: But that's like a short email. Dr. Naldi refers to new, published meta-analysis paper. So all the future investigations, all the studies, are coming from that paper, which it was cited in there.

DR. EISENMANN: Okay. Well, that wasn't clear from --

DR. ZHU: It was cited in the document. It was cited in the paper.

DR. EISENMANN: It sounded like it was coming from Dr. Naldi.

DR. LIEBLER: That's the impression I got, too.

DR. ZHU: Oh, okay.

DR. LIEBLER: Even though you did have a citation in there. The way the introduction memo was developed, from you describing the response, it sounded like it was just -- you know, you asked him,

what should an idea study be like.

DR. ZHU: So you mean we need to mention this information directly --

DR. LIEBLER: I'm not sure this even belongs in this discussion.

DR. BERGFELD: I don't think so either.

DR. KLAASSEN: Yeah. I didn't think so either.

DR. BERGFELD: I think it needs to come out. That's an academic discussion.

DR. LIEBLER: Right. For all the things that Carol says, the punch line is this really needs to go.

DR. ZHU: So, one question. Do we need to maybe discuss the different types of cancer individually? Because we have already concluded, in the conclusion section, there is no kind of relationship between hair dye user and cancer. Because for some specific type of cancer, we only have one or two studies. In that case, do we still need to discuss that specific type of cancer?

DR. EISENMANN: My feeling is that you wouldn't have to discuss each and every one. But some more general things about epidemiology.

DR. ZHU: But in the council's memo, it indicates that the discussion should clearly state that epidemiology will never prove that hair dyes do not cause cancer.

DR. EISENMANN: Right.

DR. ZHU: Do we need to include that information?

MR. GREMILLION: Dr. Naldi was brought on in response to the study showing a correlation with breast cancer specifically. Is that --

DR. LIEBLER: He was brought in to provide an epidemiologist perspective on the inconsistent body of data, with respect to breast cancer incidence and hair dye use epidemiology. So, there are some studies that indicate an association and other studies that indicate no association.

MR. GREMILLION: Yeah. I guess my point was, his comments directly address breast cancer. And so, it seems fitting that the discussion would focus on breast cancer a little bit and not --

DR. LIEBLER: Well, the discussion could certainly address breast cancer. And there's more epi data on breast cancer in hair dyes, and I think any of the other cancers.

DR. BELSITO: Bladder cancer.

DR. EISENMANN: Well, it should also be noted this doesn't contain all of the epidemiology. This is just still some of it. But there's some earlier studies, still, I believe, that are not here. The focus of this has always been since the IARC review. You picked up a few of the older studies now I believe. But I still don't think it's completely comprehensive.

DR. LIEBLER: I think our feeling is that the third paragraph of the discussion, it has the description for what would be the ideal epi study for breast cancer. It doesn't really belong here. Because we're not prescribing any other epi, basically. I think it's better for us to say that epidemiologic studies will continue, and that the panel will monitor them and continue to include them in our safety assessment.

DR. BELSITO: Yeah. But I think the discussion goes off base, because breast cancer is only one of the endpoints that we looked at. And it's the only thing in the discussion, number one. And number two, do we need a discussion at all? I mean, we've looked at all the data. And there's sort of the discussion as part of the data we look at. And then it's just a conclusion; as we state, the data do not support it. I mean, why do we need a discussion at all for this statement?

DR. SNYDER: So I wanted to eliminate almost all of the discussion. And only just state -- this is our discussion. It's not Dr. Naldi's, it's our discussion. And so, I thought we should start off by saying that we continue to do our due diligence, periodically reviewing the literature. And then these studies came up. We reviewed these studies. We had an expert look at them, and advise us if there was any issues. And they are problematic as all the previous epidemiologic studies are, with compounding factors, and other issues related to phenotype, genotype, and all the things we discussed before. But that can be very general or broad statements.

And then I thought we needed to revise the conclusion because, I think, the conclusion we can't use vague terminology. So, I mean, that we reviewed the currently available hair dye epidemiology, and

they do not provide sufficient evidence for association.

And then we can't say, "and other findings." That's too vague a language. I think we should use some specific language. Like what are the other findings, like genotype, phenotype; which, I think, is what you're meaning in the second sentence. So you could actually bring that into the conclusion, first sentence. And just have one succinct statement saying that, again, "we review the current literature. Their association are weak at best."

I wouldn't put even that. And I wouldn't put anything in there about the ideal epidemiologic study, because that's our discussion, we're not qualified to put that out there. And I don't think that we want to promote other studies to be done. We're evaluating the literature as it becomes available, periodically.

DR. BELSITO: I didn't think we needed the discussion, or the second sentence of the conclusion. Because the second sentence of the conclusion is basically the first sentence, that the data do not provide sufficient evidence. And that the panel noted there are no consistent pattern of genotype/phenotype influence, period.

MR. GREMILLION: I guess I'm surprised because I felt like the discussion was meant to underscore some of the uncertainty. I was going to push back, looking back at Dr. Naldi's comments. There's this line in the second paragraph of the discussion, "based on the available human evidence, personal use of hair dyes is unlikely to be an important risk factor for breast cancer." And then it goes on.

And Dr. Naldi's comments, he follows that up with, "however, of particular concern are two recent studies pointing to an increase risk in different ethnic groups and populations." I think that's helpful to underscore some of the uncertainty out there; and to highlight at least, in those studies, there was this association found.

DR. BELSITO: But if you're going to do that, we're focusing on breast cancer. The one cancer that's been somewhat more linked, in terms of hairdressers, is bladder cancer, and we're not discussing that at all. We basically would have to reiterate everything we've already said, pointing out that non-Hodgkin's lymphoma, bladder cancer, breast cancer, glioma, da-da-da, da-da-da, da-da-da.

For some reason Dr. Naldi elected to focus only on breast cancer, which really comes out of a single paper that looked at African American women having higher rates of breast cancer in association with hair dye. For which there was very little data as to the hair dye. And the thought, I think, there was obviously this is a dark color hair, this is para-phenylenediamine or whatever.

And people have always looked at hair color, dark or light. But I just don't think that a position paper like this, we basically -- the discussion is contained in each of the different cancer endpoints we looked at. And so, we've looked at each of the cancer endpoints. We've had the discussion in there.

And then all we need is a conclusion from that, is when you look across all of the different types of cancer endpoints, from bladder, to prostate, to glioma, da-da-da, the data is insufficient. There does not seem to be an association with any of these. That's our conclusion.

DR. GREMILLION: His comments talk about different ethnic groups and populations, African Americans, white American women, Finnish women. So, he's referring to more than just one study of African American women.

DR. BERGFELD: Can I ask a question? Is it your inference, Carol, that we should go back and collect those old reviews and put them in here? Because you said we didn't have them.

DR. EISENMANN: No. I don't think it's necessary. You're relying on the IARC review for the older studies, which I think is appropriate. I'm not sure that you would want to go back and look at all the older studies. You're looking from the IARC on. Except for, I think, we went back a little bit for the breast cancer studies. That was the intent from IARC on.

DR. BERGFELD: Do you have anywhere we say that?

DR. EISENMANN: Yeah. It says it in the introduction, I believe.

DR. KLAASSEN: I can look. On page 53.

DR. LIEBLER: I think I support deleting the discussion; trimming the second sentence out of the conclusion, and finalizing the document.

DR. BERGFELD: As a 2018 document?

DR. LIEBLER: Yes.

DR. BERGFELD: And anywhere do we have that date into this document? Is it going to be led by 12/2018 on the source document, the title?

MS. FIUME: Yes. It's on the front page of it. PDF Page 52 is the front page for the resource document; and that will have the date on it there.

DR. BELSITO: So, Dan, what are you telling me about what you want to do with the discussion? Where are you saying that -- in the introduction, that this was to be a focus on breast cancer?

DR. LIEBLER: No. No. I was referring to PDF Page 59, which is all yellow-highlighted discussion; which included that description of a putative ideal epi study for breast cancer. That entire discussion's about breast cancer.

DR. BELSITO: Right.

DR. LIEBLER: And I think that's inappropriate in this document.

DR. BELSITO: That it's what?

DR. LIEBLER: That it's inappropriate in this document.

DR. BELSITO: Yeah. Well, that's what I was saying.

DR. LIEBLER: So, I'm basically agreeing with you. I was sort of seconding what I took to be your suggestion of what to do with this. Is that we take out the discussion and we take out the second sentence of the conclusion?

DR. BELSITO: Yeah. And just in the conclusion say that we will continue to monitor data.

DR. LIEBLER: Correct.

DR. BELSITO: I was the one who recommended Luigi. I forget why Bart sent out an email looking for an epidemiologist. Was it specifically for the breast cancer study? What did he ask Luigi to do?

MS. FIUME: I don't remember. Jinqiu, do you know what was asked?

DR. ZHU: Specifically, for breast cancer. I remember.

DR. LIEBLER: We had the largest body of data, and it was the one where we felt there was inconsistency that needed to be addressed by the panel. And we didn't feel that we were -- amongst the panel, ourselves, we had the right expertise to deal with that question.

DR. BELSITO: And his response was, based on the available data that there did not appear to be a causal relationship. And then he went on to this big thing about, well, to really know you need to do this huge --

DR. SNYDER: We need 356,000 patients, with these criteria, blah, blah, blah.

DR. BELSITO: Right. So, we got his answer; that, at least, based upon the data that exist today, there appears to be no causal relationship.

DR. LIEBLER: Right. I think it was either -- in the previous iteration of this document, because either a comment from somebody on the panel, or possibly from the council, I don't remember which, saying it would be better to say what should be done. Or it would be useful to say what should be done. I don't remember where that came from, but I do remember the request from somebody.

And that led to this discussion, I think, particularly, the third paragraph of this discussion. But basically saying, a huge, super, uber, epi study is not going to -- first of all, it won't ever happen. And even if it did, it probably won't answer the question beyond any possible doubt.

MR. GREMILLION: I guess just reading Dr. Naldi's study, and the concise summary statements there he has -- the first sentence, "the available evidence linking hair dye use and breast cancer is limited, but warrants further investigation." I remember in a previous meeting we had, the available -- just the first clause of that sentence.

And I feel like it's a similar -- even though they're set out in two sentences, it's a similar kind of package of statement. Saying, based on the evidence, it's unlikely to be an important risk factor; however, of particular concern are these studies. And then he concludes with the need for a systematic review.

DR. SNYDER: I took that in the context of his expertise as an epidemiologist. This is our

document. And so, in the context of the data that we review, we have not been provided any substantive data to make us be concerned. And we don't really want to be -- we want to be cautious about promoting studies, because then somebody says, well, what kind of study? And we're not qualified to do that. And so, again, I think that's what we're trying to do.

MR. GREMILLION: It is. And honestly, if the discussion section gets deleted altogether, it's a moot point. But my objection was just having that, based on the available with human evidence sentence, without the following sentence, that seems to hedge it a little bit.

DR. SNYDER: I think that's what Don was saying in the conclusion we have, that to date there's no human data to support a cause and effect relationship.

MR. GREMILLION: Yeah. I mean, specifically in the discussion he's cited for that first line. But yeah, I understand you have your own analysis and you're going to present it.

DR. BELSITO: But I mean, he takes and he says, okay, the ideal epidemiologic study to evaluate breast cancer. Then we should say, the ideal epidemiologic study to evaluate lymphoma. The ideal epidemiologic study to evaluate bladder cancer. The ideal epidemiologic study to evaluate glioma. We could go on and on and on.

And basically, I think that our point is, we've looked at all the studies, there doesn't seem to be a causal relationship; but, we will continue to monitor everything that comes out in the literature. That's all we can do.

MR. GREMILLION: I don't want to say a description of the needed study needs to be in there. I'm not familiar enough with these reports. But I do think that there's a basis for singling out breast cancer, based on the same factors that led you to get Dr. Naldi in the first place.

DR. BELSITO: Again, I think if we're going to single out a cancer, we'd single out bladder cancer.

MR. GREMILLION: The studies on that are for the workers.

DR. BELSITO: The studies for users do not show a causal relationship. But there is suggestoid (phonetic) evidence for hairdressers.

DR. SNYDER: Certain genotypes.

DR. BELSITO: Certain genotypes for hairdressers. And there's also the confusion with a confounder of smoking, which is also known to be carcinogenic. And the same thing came up in the textile industry when it was in the US. Textile dye workers, and smokers, and bladder cancer in that industry. So there's suggestoid evidence for those groups.

So, if there's any cancer that seems like it could be related to dye, it would be bladder cancer, more than breast, or lymphoma, or prostate. Because you never really saw prostate cancers coming up in the textile workers, who were largely men.

I just think that by putting this discussion in at all, I mean you just have to go on, and on, and on to look at all the cancer types.

DR. SNYDER: Well, I think you said, earlier, that this discussion, much of it could go under the breast cancer, dealing with that new study that we raise our first concern. So, it's not like we're going to throw it all out. It's just that it's not appropriate in a discussion for an overarching document to just focus on one cancer.

I think we can take some of that language and move it under the breast cancer, particularly, in relationship to the interpretation of that study that showed something that we were not comfortable with interpreting. And that's why we had the expert come in.

DR. BELSITO: Actually, that's a good point. I mean, this goes under the breast cancer part, not a discussion for the entire document. And can be condensed a little bit.

MS. FIUME: I think Jinqiu can take the suggestions given and then rework the document a little bit. And remove the discussion and make it what you want it to be.

DR. ZHU: Yes.

DR. BELSITO: I don't think there is a discussion to this document. The discussions occur in each of the sections of cancer.

MS. FIUME: Right. Move it from the discussion into the cancer section. Because in the past

versions, whatever we've included in the report, we've never specified a specific cancer. It was just hair dye and cancer. It was never any type of specific cancer mentioned. In the wordings of our reports, we always refer to our resource document, which we will do as normal. But we've never specified any type of specific cancer, in either the summary or the discussion sections.

DR. SNYDER: My only comment was that I thought it was a good mechanism to make the reader aware. They don't have to read through all of the cancer publications to see where we're at, as far as how current are we.

So, I thought it was okay to have a brief discussion that said we've identified -- since 2014, the last time it was reviewed, we've identified these five additional studies, they were considered, and just leave it at that. And the conclusion is still what it is.

I just thought that was maybe a good way to let the reader know what we looked at and some interested party could say, well, you missed this study or something.

DR. BELSITO: Okay. So this will come back to us once again?

MS. FIUME: Yes. For a final, final look.

DR. BELSITO: Okay.

DR. BERGFELD: Will it go out for comment again?

MS. FIUME: Did it go out for comment last time, Jinqiu, or are we waiting until we get it all finalized? I guess it did go to comment because it's a public document. I forget how it worked. I'll check and see what we did and we'll follow the same protocol.

DR. BERGFELD: Yeah. I think it goes for comment.

Day 2 of the December 3-4, 2018 Expert Panel Meeting – Full Panel

DR. BELSITO: It was my request that we update this, simply, because we hadn't updated it for a while and there was new information out. I think the particularly more disturbing one was the apparent higher rates of breast cancer in African-American women, using hair dyes, versus non-African American.

We had asked Dr. Luigi Naldi, from Bergamo, Italy, to look at that data. Overall, he did. And he found that the available evidence, linking hair dye use and breast cancer, was limited; although, he did feel that required further investigation. At this point, he said, based upon the available evidence, he was not seeing a link.

Our only concern was that his report ended up in the discussion, as a full report, dealing only with breast cancer, and that's not the only cancer we're concerned about. We had recommended that that entire highlighted area in the discussion be deleted, and just sort of summarize; that based upon the available evidence, there is no apparent causal link between consumer hair dye use and carcinogenic endpoints of any kind.

DR. BERGFELD: Any comment?

DR. MARKS: Yeah, we agree, wholeheartedly, with what you suggested, Don. Let's go to Page 60 of the document. Because the other thing that we felt, that the conclusion on Page 60, that the last two sentences on the conclusion were not necessary. So, our conclusion would be just, that the epidemiology data do not provide sufficient evidence for causal relationship between personal hair dye use and cancer. And delete the second two sentences. We felt that they didn't add anything and, in fact, they may confuse the issue.

DR. BELSITO: I don't have a problem with that, team? Okay. The only other thing to mention, in the discussion is, obviously, that we will continue to monitor this. And as new studies come out, we will look at them and reevaluate our conclusions.

DR. BERGFELD: The question I had of Bart is, if the team members on both sides or the whole panel are agreeable to these changes, that have been made, is this document ready to be posted? Or do we want to look at it one more time in April? This should be on a calendar review, at least every two years; and, obviously, if a report comes up, we should look at it right away. So, what is your suggestion?

DR. BELSITO: I think the changes we're asking for are so minimal, that this can go out as a final.

DR. BERGFELD: Okay. Jim.

DR. MARKS: I would second that. And, I guess, one of the reasons we deleted the discussion was because it wasn't broad enough and such. If we're reviewing new epidemiologic papers, or studies, as they occur, that do we really need the review -- that should be added to the document, ongoing, I would think, just like both in the text and in the table. And for us, every two years, to go back and look at this unless something really changes our conclusion. I don't know if two years is right or five years. Two years might be too often, but I don't know.

DR. BELSITO: I think we have a group of experts in various areas that will be picking up data. And if there's a substantive paper, that comes out, we should not wait two or five years. It should be brought to the attention of the panel. And then the decision can be made, based upon that, whether we need to update the document, or it can be held. But I don't think we should set timelines for this; because this is a very critical, topical, issue that needs to be monitored.

DR. MARKS: I agree with that approach, Don. I was just thinking you go from the beginning to the end with the document. I think that will occur naturally, as the new studies come in; and then they just get added to the document.

DR. BERGFELD: Well, one of the problems that we've had, historically, is that unless there is a big article or some publication that brings it to light that we need to look at, this particular document gets buried a little bit because of the workload internally. So, at least, if it's on the calendar, someone will take a look, quickly, at what's out there, so that we don't miss anything. That's something that can be decided internally how they're going to do that.

I'd like a consensus show of how you'd like to deal with this. And what I've heard is that it's ready to go and be posted. Is that correct?

DR. MARKS: That's correct.

DR. BERGFELD: All right. So, we'll do that. So, this will not appear in April. The next one is aerosols in inhalation. Dr. Marks giving his opinion and his team's opinion.

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

Expert Panel Resource Document

Hair Dye Epidemiology

03/2021 - DRAFT

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This resource document was prepared by Jinqiu Zhu, Ph.D, D.A.B.T., E.R.T, CIR Toxicologist.

BACKGROUND

Hair dyes may be broadly grouped into oxidative (permanent) and direct (temporary or semi-permanent) dyes.[1] The oxidative dyes consist of precursors mixed with developers to produce color, while direct dyes consist of preformed colors. In contrast to permanent and semi-permanent dyes, temporary dyes cover the surface of the hair but do not penetrate into the hair shaft. Epidemiology studies that seek to determine links, if any, between hair dye use and disease provide broad information and have been considered by the Expert Panel for Cosmetic Ingredient Review (Panel), although these studies do not specifically address the safety of individual hair dye ingredients.

The Panel reviews new epidemiological studies addressing the personal use of hair dyes as these studies become available. Table 1 summarizes the studies specifically addressing bladder cancer, lymphoma, leukemia, prostate cancer, testicular cancer, and breast cancer. Relevant meta-analytical studies included here address glioma and breast cancer, in addition to bladder and blood cancers. Occupation as a hairdresser, barber, or cosmetologist involves exposures to multiple products used during work, making it difficult to use the results of such studies to inform the assessment of the risk, if any, associated specifically with hair dyes. Accordingly, such studies are not summarized here.

The Panel considers that epidemiological studies, when based on better information about exposure, can provide more useful findings than other such studies. According to one study, exposure assessments in hair dye epidemiology studies ranged from minimal information (e.g., ever/never use) to subject-recalled information on type, color, duration and frequency of use.[2] A scale from + to ++++ has been developed to rate the quality of hair dye exposure assessments in hair dye epidemiology studies, as shown below. This scale was used to score the studies that are summarized in Table 1.

+: Assessed ever/never use;
++: Assessed the type of hair dye, *or* dye type plus dye color or duration, *or* with information on two or three other factors (color, frequency, duration), but no information on type;
+++: Assessed dye type, color, *and* frequency *or* duration of use;
++++: Assessed all four critical aspects: hair dye type, color, duration, and frequency of use

An International Agency for Research on Cancer (IARC) working group summarized the relevant epidemiology studies and observations on breast, bladder and hematological cancers.[3,4] The working group concluded that the animal studies provided limited evidence for the carcinogenicity of hair colorants, and the data are of insufficient quality, consistency, or statistical power to establish the presence or absence of a causal link between personal use of hair dyes and cancer. Based on a lack of evidence from studies in people, IARC considers personal hair dye use to be "not classifiable as to its carcinogenicity to humans."[1] In addition, occupational exposure during work as a hairdresser, barber, or beautician was assessed. The working group found that exposures from these occupations are probably carcinogenic, based on limited evidence of increased risk for bladder cancer in hairdressers and barbers. (The evidence for other types of cancer is considered mixed or inadequate.) However, occupational safety is outside the scope of the work of the Panel.

The studies herein result in either an odds ratio (OR) or a relative risk (RR), two similar but not synonymous terms. An OR represents the odds that an outcome (e.g., cancer) will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure; whereas a RR is a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group.[5,6] In epidemiological research, ORs are most often used in case-control (backward looking) studies, and RRs are used in prospective (forward looking) studies, such as cohort studies and clinical trials. An OR or RR of 1 means there is no difference between two groups in terms of risk following a particular exposure; an OR or RR < 1 means that the exposure may reduce the risk of cancer (possibly protective), while OR or RR > 1 means the exposure may increase the risk of cancer (possibly causal). Broadly equivalent to RR, hazard ratio (HR) is applied when the risk is not constant with respect to time. It uses information collected at different times to simply compare two hazards.[7] A HR not equal to 1 indicates that two events are not occurring at an equal rate, and the risk of an event in one group is different than the risk of an event in another at any given time interval. The 95% confidence interval (CI) is used to estimate the precision of the OR or RR. If a 95% CI for the relative risk includes the null value of 1, then there is insufficient evidence to conclude that the groups are statistically significantly different.

The following provides a brief summary of many relevant epidemiological studies that have been published since about 2010, as well as older epidemiological studies that were included in comprehensive reviews, such as that published by the IARC in 2010.[4] The Panel determines to continue monitoring upcoming epidemiological data on the link between personal use of hair dyes and cancer risk and the conclusion of the document would be re-evaluated based upon the new information on a regular period basis.

STUDY SUMMARY

A prospective cohort study was performed recently to comprehensively investigate the relationship between cancers in US women and use of permanent hair dye.[8] The participants included 117,200 women enrolled in the Nurses' Health Study who were free of cancer at baseline. During 36 years of follow-up (between 1976 and 2012), a total of 20,805 solid cancers and 4,860 cancer related deaths were documented. Data collection on permanent hair dyes use are detailed in duration of use (non-user, < 5 years, 5 - 9 years, ≥ 10 years); frequency of use (non-user, every ≥ 5 weeks, every 1 - 4 weeks); cumulative dose (non-user, 1 - 99 times, 100 - 199 times, ≥ 200 times); age at first use (non-user, < 30 years, ≥ 30 years); and time since first use (non-user, < 30 years, ≥ 30 years). Overall, no association was identified between ever users of permanent hair dyes and risk of solid cancers under investigation (HR 0.98, 95% CI: 0.96 - 1.01). Specifically, there is no significant increases in risk of the following cancer types: cutaneous squamous cell carcinoma (HR 1.00, 95% CI: 0.93 - 1.09; n = 2,792), bladder cancer (HR 1.05, 95% CI: 0.90 - 1.24; n = 596), melanoma (HR 1.01, 95% CI: 0.89 - 1.14; n = 1,198), breast cancer (HR 1.02, 95% CI: 0.98 - 1.07; n = 9,252), brain cancer (HR 0.72, 95% CI: 0.56 - 0.93; n = 277), colorectal cancer (HR 1.05, 95% CI: 0.97 - 1.14; n = 2,394), kidney cancer (HR 1.03, 95% CI: 0.85 - 1.23; n = 477), lung cancer (HR 0.9, 95% CI: 0.87 - 1.01; n = 2,623), ovarian cancer (HR 1.09, 95% CI: 0.97 - 1.22; n = 1,215), and hematopoietic cancer (n = 1807); while basal cell carcinoma risk was slightly increased for ever users (HR 1.05, 95% CI: 1.02 - 1.08; n = 22,560). Additionally, ever users did not have an increased risk of cancer related deaths (HR 0.96, 95% CI: 0.91 - 1.02). Interestingly, self-administered questionnaires indicated hair dye ever users were more likely to be smokers and consumed more alcohol than those reporting no permanent hair dye use. But the authors also claimed that the generalizability of current findings is limited to white US women and might not extend to other populations. This hair dye exposure assessment was +++ on the Rollison et al. (2006) scale.

Bladder Cancer

In a meta-analysis involving 15 case-control and 2 cohort studies, the abstracted information included the variables adjusted and/or used to match control subjects with cases.[9] For example, 12 of the studies clearly adjusted for smoking; adjustment for smoking was not clear in 1 study. The pooled RR of bladder cancer incidence/mortality was 0.93 (95% CI: 0.83 - 1.05) for personal use of any type of hair dye, compared with no use, and comparable results were obtained when the subjects were stratified by sex. The RR for personal use of permanent hair dyes from 7 of the studies was 0.92 (95% CI: 0.77 - 1.09). Similarly, no association was found between bladder cancer and the duration or lifetime frequency of use of any type of hair dye or use of permanent hair dyes, compared with never used hair dyes. The RR for the use of dark-color hair dyes was 1.29 (95% CI: 0.98 - 1.71).

In a population-based case-control study conducted in the Netherlands, no association was found between bladder cancer and ever use of permanent hair dyes (OR 0.87; 95% CI: 0.65 - 1.18) or temporary hair dyes (OR 0.77; 95% CI: 0.58 - 1.02).[10] Similarly, no association was observed when hair dye use was defined by type, duration or frequency of use, dye color, or extent of use or when the patients were stratified by aggressive and non-aggressive bladder cancers. The subjects were 246 cases and 2,587 controls; all of the subjects for which the analyses were performed were women (less than 5% of the men selected for the study reported ever using hair dyes). All analyses were adjusted for age and smoking status, duration and intensity. Additional adjustment for education level and other variables considered were not included in the final model because they did not change the standardized regression coefficient (β) by more than 10%. The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale.

A population-based case-control study was conducted in Maine, Vermont, and New Hampshire.[11] The subjects were 1,193 cases of urinary bladder cancer diagnosed from 2001 to 2004 (911 male and 282 female), and 1,418 controls (1,039 male and 379 female). The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. The hair dye models were adjusted for age, race, sex, and smoking status.

No association was found between ever/never use of hair dyes and bladder cancer – the OR and associated 95% CI: for women was 0.70 (95% CI: 0.50 - 1.00), and for men 0.70 (95% CI: 0.40 - 1.00). Because of the excellent exposure assessment, the authors were able to examine subsets of the population studied. Women who used red hair colors, for example, exhibited an OR of 0.40 (95% CI: 0.20 - 0.80), suggesting a significantly lower risk of bladder cancer associated with the use of such hair dyes. A similar lower risk of bladder cancer was reported for women who used hair dyes for a duration between 10 and 19 years (OR 0.5; 95% CI: 0.27 - 0.79). As the data were further analyzed, the authors considered women with and without college degrees. Women without college degrees who used permanent hair dyes exclusively, for example, had a significantly lower risk of bladder cancer (OR 0.50; 95% CI: 0.40 - 0.70). Exclusive use of permanent hair dyes by women with college degrees was associated with a significantly higher risk of bladder cancer (OR 4.90; 95% CI: 1.70 - 14.60). No statistically-significant interactions with hair-dye use were found when the data were stratified by state of residence, hair-dye product type, smoking, age at diagnosis/interview, or disease aggressiveness in the female subjects.

To investigate risk factors for bladder cancer in Iran, a population-based case-control dataset with 692 cases and 692 controls was analyzed.[12] Cases were identified using the Iranian cancer registry. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. The OR for hair dye use and bladder cancer was 1.81 (95% CI: 1.08 - 3.06). After adjustment for cigarette smoking, the OR was 1.99 (95% CI: 1.02 - 3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was found.

Prostate Cancer

A hospital-based case-control study was conducted among prostate cancer cases in Taiwan, involving 296 cases with newly diagnosed prostate cancer and 296 age-, ethnicity-, and hospital-matched controls. Information on hair dye use was obtained through a standardized questionnaire.[13] The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (adjusted OR 2.15; 95% CI: 1.32 - 3.57). The study found personal hair dye use increased risk of prostate cancer with a dose-response effect. Meanwhile, to determine the rate of prostate cancer survival, another 608 incident prostate cancer cases were investigated. Of the 608 cases, 26.4% (161/608) reported having used hair dyes. The use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths ($p = 0.753$).

This report was the first to show a positive association between personal hair dye use and risk of prostate cancer, revealing a dose-response relationship assessed by duration and frequency; however, cumulative exposure dose, a critical indicator to estimate a dose-response effect, was not assessed. The external validity of this study has been questioned.[14] Other studies targeted on hairdressers observed no increased risk of prostate cancer.[15] While Tai et al.'s findings are limited and do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted.

Lymphoma and Leukemia

A meta-analysis of 20 case-control studies of leukemia has been performed in 2017.[16] The RRs for the associated risk of leukemia were: with permanent hair dye use RR = 1.19 (95% CI: 1.07 - 1.33), with dark hair dye use RR = 1.29 (95% CI: 1.11 - 1.50), with hair dye use among males RR = 1.42 (95% CI: 1.01 - 2.00), with hair dye use pre-1980 RR = 1.49 (95% CI: 1.21 - 1.83), and with hair dye use for longer than 15 years RR = 1.35 (95% CI: 1.13 - 1.62). Overall, findings suggest that ever use of hair dye is not a significant risk factor for leukemia.

A population-based case-control study was conducted to evaluate whether the hair dye use influenced the risk of leukemia and non-Hodgkin's lymphoma (NHL) in Italy.[17] The analysis was restricted to women in the population studies because too few of the men reported any hair dye use. There were 161 cases (120 lymphoid and 41 myeloid) and 84 controls among the women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale, because only duration of hair dye use < 15 years vs. ≥ 15 years was evaluated. In a multivariate analysis, the OR was 2.3 (95% CI: 1.0 - 4.9), with $p = 0.036$ for a trend, for NHL in women using hair dye for at least 15 years. No association was found between lymphoid malignancies and tobacco smoking or the consumption of alcoholic beverages in this study.

A meta-analysis of 19 case-control studies of NHL subtypes was conducted, focusing on follicular lymphoma (FL).[18] No associations between FL and hair dye use type, duration, or frequency were found in this study, except for a modest increase in women who used hair dyes before 1980 (OR 1.40; 95% CI: 1.10 - 1.78). Many oxidative hair dye products were reformulated in the early 1980s in the US to eliminate ingredients that produced tumors in animal bioassays.[19] In comparison, the risk of FL in women was associated with current cigarette smoking, trending higher with increasing duration of smoking.

Another meta-analysis of 19 case-control studies of NHL subtypes was performed, focusing on diffuse large B-cell lymphoma (DLBCL).[20] There were no overall and sex- or age-specific associations between DLBCL and hair dye use, based on the basic adjusted model results of this study. The OR for mediastinal DLBCL was 4.97 (95% CI: 1.63 - 15.15) for use of hair dyes for at least 20 years, compared with never used hair dyes. Using hair dyes for at least 20 years was not associated with DCBCL at other anatomical sites, including the central nervous system (CNS), testis, gastrointestinal tract, and skin. Use of hair dyes for less than 20 years was not associated with DLBCL at any site. In comparison, smoking was associated with CNS, testicular and cutaneous DLBCLs in this study.

A hospital-based case-control study was conducted to investigate the hair dye use in the etiology of leukemia and lymphoma in Egypt.[21] There were 130 cases, including 23 cases of chronic lymphocytic leukemia (CLL) and 107 cases of NHL, and 130 age- and sex-matched controls. The evaluation of hair dye exposure was a + on the Rollison et al. (2006)

scale. In a univariate analysis, no statistically significant association was found between these lymphoproliferative disorders and history of using hair dyes, family history of cancer, exposure to X-rays, or smoking (χ^2, $p > 0.05$).

A hospital-based case-control study of myelodysplastic syndromes (MDSs) was performed in China.[22] There were 403 cases and 806 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. In a univariate analysis, the OR for hair dye use (≥ 2 times per year) and all MDSs was 1.46 (95% CI: 1.03 - 2.07). In a multivariate analysis performed to adjust for potential confounding factors, the OR was not statistically significant (OR 1.31; 95% CI: 0.88 - 1.93). In comparison, smoking was associated with the development of MDSs in the univariate analysis and with refractory anemia with excess blasts (RAEB) in both the univariate and multivariate analyses.

A hospital-based case-control study was conducted on 649 NHL cases in Shanghai.[23] The analysis included 1,298 controls and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. No increased risk of NHL was reported (OR 0.93; 95% CI: 0.75 - 1.16). For CLL and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use (OR 0.37; 95% CI: 0.18 - 0.76). In comparison, alcohol consumption and cigarette smoking were not associated with NHL in this study, although smoking ≤ 20 years (but not > 20 years) was associated with precursor B-cell neoplasms.

Tissue samples from a NHL case-control study in males from Iowa and Minnesota were subjected to re-evaluation using FISH (fluorescence in situ hybridization) cytogenetic technique to examine both *t*(14;18)-positive and *t*(14;18)-negative NHL subtypes and IHC (immunohistochemistry) assays to evaluate expression of the anti-apoptotic protein bcl-2.[24] There were 8 *t*(14;18)-positive, 12 *t*(14;18)-negative, 20 bcl-2 positive, and 4 bcl-2 negative NHL cases and 58 control subjects in the subpopulation tested (i.e., men having used hair dye at least once a month for at least one year, or occupational exposure to hair dyes on any job held for at least a year). The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. Adjusting for age, state, and proxy status (i.e., whether or not next-of-kin proxies were interviewed), a statistically-significant association between ever/never use of hair dyes and *t*(14;18)-negative NHL (OR 2.90; 95% CI: 1.60 - 5.00) and bcl-2 positive NHL (OR 2.20; 95% CI: 1.40 - 3.40), but not with *t*(14;18)-positive NHL (OR 1.30, 95% CI: 0.60 - 2.60) or bcl-2 negative NHL (OR 1.40; 95% CI: 0.50 - 3.80). Similarly, smoking was associated with *t*(14;18)-negative NHL, but not clearly associated with *t*(14;18)-positive NHL, bcl-2 negative NHL, or bcl-2 positive NHL in this study.

A hospital-based case-control study of acute myeloid leukemia (AML) was conducted in Shanghai.[25] The investigation consisted of 722 newly diagnosed AML cases and 1,444 individually gender-age-matched patient controls at 29 hospitals in Shanghai. The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. There was no increase in the risk of AML and personal use of hair dyes; The OR was 0.98 (95% CI: 0.8 - 1.2). In contrast, there was an association between AML and smoking, particularly among the male subjects, as well as alcohol consumption and a low level of education in this study.

A hospital-based case-control study was conducted among acute lymphoblastic leukemia (ALL) cases in Iran, involving 125 cases (age younger than 15 years) and 130 controls matched with age, gender, and residence location.[26] No significant association was observed between the risk for ALL and mother's use of hair dye during pregnancy (OR 0.87; 95% CI: 0.32 - 2.37). The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale.

A hospital-based case-control study was performed in Pakistan.[27] The analysis comprised 25 adult leukemia cases with 50 gender- and marital status-matched healthy controls, and 40 children cases with 80 age- and gender-matched healthy controls. Increased leukemia risk was observed among hair dye users. The un-adjusted OR was 4.14 (95% CI: 1.28 - 4.95) for adults and 4.60 (95% CI: 1.57 - 4.60) for children, respectively. Other factors significantly relevant to leukemia status included exposure to chemical factory, a positive family history of leukemia, a positive trauma history, etc. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale.

A hospital-case-control study was carried out in China to investigate the relationship between childhood leukemia and breastfeeding.[28] The subjects included 958 cases (580 boys, 378 girls) and 785 controls (449 boys, 336 girls) within the period between 2008 and 2017 at the Children's Hospital of Zhejiang University. Multivariable regression analysis indicated that parents use of hair dye during breastfeeding was a significant risk factor for childhood leukemia (OR 13.56; 95% CI: 1.11 - 165.20). In addition, multiple other factors were identified to be associated with increased risk of childhood leukemia, such as smoking during pregnancy, a history of using birth control pills before pregnancy, abortion history, and mothers having lower education level. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale.

A meta-analysis aimed at analyzing the association between hair dye use and the pathogenesis of non-Hodgkin's lymphoma (NHL) was conducted in 2019, including 13 case-control studies and 3 cohort studies published between 1988 to 2015 with 720,019 participants.[29] The 13 case-control studies included a total of 10,399 patients and 20,013 controls and the 2 cohort studies reported 928 NHL cases. The OR value of the case-control studies or cohort studies was 1.13 (95% CI: 0.86

- 1.84) or 1.16 (95% CI: 0.91 - 1.69), respectively. But when all studies were combined, the OR value was 1.14 (95% CI: 1.01 - 1.29), indicating that the risk of NHL in a high population of hair dye users was 14%. In addition, the duration of hair colorant use recorded in these studies was divided into 3 groups: < 10 years (OR 1.19; 95% CI: 0.90 - 1.88), 10 - 20 years (OR 1.20; 95% CI: 1.02 - 1.95), and > 20 years (OR 1.34; 95% CI: 1.04 - 1.92). The results suggested that people who used more than 20 years of hair dye had increased risk of NHL.

In a meta-analysis involving 5 case-control studies, the association between history of hair dye use and risk of FL was assessed within a total of 4,687 cases and 30,137 controls.[30] The period of data collection spanned 1976 - 2009. Hair dye use before 1980 was positively associated with FL risk (RR 1.66; 95% CI: 1.22 - 2.25) and no evidence of effect was observed after 1980.

Glioma

A meta-analysis including 4 case-control and 2 cohort studies of personal was conducted to investigate the hair dye use and the incidence of gliomas.[31] Matching or adjustment for age and sex was performed in all 6 studies included in this meta-analysis, and for smoking in 2 of the 6 studies. The most adjusted risk estimates were included, and the raw data were used when adjusted estimates were not available. Summary RRs for ever use of any hair dyes were 1.13 (95% CI: 0.89 - 1.45) for all studies, 1.29 (95% CI: 0.94 - 1.78) for case-control studies, and 0.90 (95% CI: 0.78 - 1.05) for cohort studies. Similar results were obtained when the subjects were stratified by geographic regions and sex. No significant associations were found among the studies that evaluated permanent hair dye use and duration of any hair dye use.

Testicular cancer

A case control study was carried out among 527 mothers of testicular germ cell tumors (TGCT) cases and 562 mothers of controls.[32] The subjects were enrolled in US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) study between 2002 and 2005. TGCT, accounting for approximately 98% of testicular cancers, are the most commonly occurring cancer among men aged 15 - 44 in the US though they are rare tumors in the general population.[33] Maternal use of hair dye (OR 0.80; 95% CI: 0.54 - 1.18), hairspray (OR 1.17; 95% CI: 0.89 - 1.55), or permanent wave (OR 1.18; 95% CI: 0.86 - 1.62) was not associated with TGCT risk in sons. The hair dye exposure assessment was a ++ on the Rollison et al. (2006) scale.

Breast Cancer

In a case-control study conducted in the metropolitan New York City area and in ten counties in New Jersey (NJ), involving both African Americans and White women, breast cancer cases were identified by multiple sources, including hospital charts and NJ cancer registry.[34] The subjects were 1,508 African American and 772 European American cases (52 ± 10.7 and 52.0 ± 10.0 years old, respectively) and 1290 African American and 715 European American age- and county-matched control subjects (50.9 ± 10.3 and 49.8 ± 8.7 years old, respectively). The evaluation of hair dye exposure was ++++ on the Rollison et al. (2006) scale. Final OR estimates were adjusted by age, education, body mass index, family history of breast cancer, and oral contraceptive use. In the control group, about 30% of African Americans and 58% of Whites reported regular use of hair dyes. Overall, ever use of hair dyes and duration of use were not significantly associated with increased cancer risk in both African Americans and Whites. Among African Americans, an increased risk of breast cancer was documented for the use of dark hair dye shades, and for salon application of dyes, adjusted OR being 1.52 (95% CI: 1.21 - 1.91) and 1.26 (95% CI: 1.00 - 1.58), respectively. In Whites, an increased risk was documented for dual use of relaxers and hair dyes with OR 2.40 (95% CI: 1.35 - 4.27), the wide CI reflecting the limited number of exposed women. When considering the estrogen receptor status of cancer, the risk of estrogen positive breast cancer was increased in African Americans with a higher frequency of hair dye use (OR 1.36; 95% CI: 1.01 - 1.84) and in Whites with the use of dark hair dye shades (OR 1.54; 95% CI: 1.01 - 2.33). These differences in risk profile between African Americans and Whites are not easy to reconcile. They may reflect different patterns of use, or represent chance effects due to multiple testing. In this study, women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter. Replication of results by an independent study is needed. Ideally, such a study should be able to ascertain the type of hair dye product used and its timing of use.

A population based case-control study in Finland recruited a total of 6,567 breast cancer patients diagnosed between 2000 and 2007 and 21,598 age-matched controls.[35] The evaluation of hair dye exposure was a +++ on the Rollison et al. (2006) scale. The recruitment of patients was based on a nation-wide cancer registry covering almost 100% of solid tumors. The exposure of primary interest was the use of hair dyes with detailed information on the cumulative lifetime number of hair dye episodes, age at first use, and the types of dyes used. When calculating ORs, potential confounding factors, namely

parity, age at first birth, family history of breast cancer, menarche age, use of hormonal contraceptives, physical activity, alcohol use, body mass index and education, were included in a stepwise regression model. Bias-adjusted ORs were calculated as well. A large proportion of women reported ever use of hair dye products, with rates increasing from 84% in women born before 1950 up to 92% in women born in or after 1960. The odds of breast cancer were significantly increased when comparing ever vs never users of hair dyes (OR 1.23; 95% CI: 1.11 - 1.36).

Early age at first dye (20 - 29 years) was associated with higher odds of breast cancer when compared to late age at first dye (40 years or later) (OR 1.14; 95% CI: 1.05 - 1.25). When considering ever use vs. non-use, the ORs were increased with all the different types of hair dyes, the highest estimates being obtained for women who reported to have used temporary and/or semi-permanent dyes, ORs being 1.32 (95% CI: 1.16 - 1.52) and 1.31 (95% CI: 1.17 - 1.46), respectively. Latency of effect was suggested by the fact that the OR for cumulative hair dye use was the highest among women born between 1950 and 1959. When considering the cumulative number of hair dye episodes, the OR ranged from 1.07 (1 - 2 dye episodes) to 1.28 (10 - 34 dye episodes) and 1.31 (35 - 89 dye episodes), and then decreased to 1.25 (≥ 90 dye episodes). The ORs did not change when smoking was included in the multivariate analysis.

One meta-analysis summarized results of studies conducted from 1966 up to 2005,[15] and included 12 case-control studies, which involved a total of 5,019 cases and 8,486 controls, and 2 cohort studies which recruited a total of 1,135 incident cases of breast cancer. The pooled RR of breast cancer was 1.06 (95% CI: 0.95 - 1.18) and nonsignificant when comparing ever use vs. never use of hair dyes. No significant increased risk was documented when considering intensive exposure or restricting analyses to the use of permanent dyes only. It is noted that, giving the largely prevalent use of hair dyes in the population, frequency of use rather than simple distinction between users and nonusers, would be relevant to consider.

In a cohort study conducted in the framework of the Shanghai Women's Health Study, a total of 75,221 women completed a baseline survey between 1996 and 2000 and were followed up to 2005.[36] A total of 358 incident cases of breast cancer were identified. In the sample, 29,076 women (39.6%) reported ever using hair dye and a total of 358 incident cases of breast cancer were identified. The average number of person years was 7.31. The RR for breast cancer in hair dye users vs non-users, adjusted by age, education and smoking, was 0.93 (95% CI: 0.78 - 1.09). No relation was documented between duration of hair dye use and risk of cancer. Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale.

A case-control study was conducted, including 191 breast cancer patients interviewed in a hospital in 1975 - 1976 in Oxford, UK, with 561 aged matched controls without cancer (within three years), marital status, and social class.[37] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. Seventy-three cases and 213 controls had used permanent or semi-permanent hair dyes, giving an RR of 1.01. There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.

A case-control study consists of 50 breast cancer patients at a cancer treatment center with 100 hospitalized controls in London, Ontario, and 35 breast cancer cases with 70 neighborhood controls in Toronto, Ontario.[38] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The RRs for breast cancer from use of permanent hair dyes (at any time) were 1.30 (95% CI: 0.60 - 2.50) in London and 1.10 (0.50 - 2.40) in Toronto. Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.

A case control study was performed among 398 breast cancer patients at a screening center between 1977 and 1981 in New York City, with 90 randomly selected, age matched controls.[39] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The OR for breast cancer from use of permanent hair dyes (at any time) was 0.80 (95% CI: 0.60 -1.10). There was also no evidence of a trend in risk with increasing number of hair dye uses (38% of the subjects had used hair dye at least 100 times, while 77% had used hair dyes at least once). An analysis of breast cancer risk from 5 or more years of work as a beautician was also compared. Although personal hair dye use was unrelated to breast cancer risk, the OR for beauticians was 3.00 (95% CI: 1.10 - 7.80).

A hospital-based case-control study of breast cancer was conducted on 1,052 women in Iran.[40] The evaluation of hair dye exposure was + on the Rollison et al. (2006) scale. There were 526 newly diagnosed breast cancer cases, with 526 age-matched controls randomly selected in Namazi Hospital between November 2014 and March 2016. The study showed that multiple factors were associated with the risk of breast cancer, such as hair coloring, age at first delivery, stress, and smoking. The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI: 1.41 - 2.62). However, the design of the study was not able to confirm a causal association between any investigated variables and breast cancer.

A meta-analysis was performed to investigate the association between hair dye use and breast cancer, including 8 case-control studies published between 1980 and 2017 with a total of 38,037 participants.[41] Of the 24 studies initially considered relevant, only 8 were considered to meet the authors' selection criteria, including the five prospective studies that did not show any association between hair dye use and breast cancer. The prospective studies were excluded for various reasons: HR instead of an OR/RR was used, the death rate instead of cancer incidence was recorded, no information on the number of controls was provided, and the study had a high focus on other types of cancer. Using a random effects model the pooled RR for women using hair dyes was 1.18 (95% CI: 1.03 - 1.37), which indicates an 18.8% increased risk of future development of breast cancer among hair dye users. However, the authors also stated that the reliability of this systematic analysis had decreased due to the large number of excluded prospective studies. Importantly, the limited exposure information in the eight analyzed studies did not allow for any conclusion related to dose-response (either duration or frequency of use), or type of hair dye.

A national prospective cohort study was carried out to examine the association between hair dye and straightener use and breast cancer risk by ethnicity.[42] Study participants were 46,709 women aged 35-74 and came from all 50 states in the U.S. and Puerto Rico. Subjects included women who did not have a breast cancer diagnosis at the time of study recruitment (between 2003 - 2009) and who had 1 or more sisters diagnosed with breast cancer. Compared to nonuse, use of permanent dye was associated with 45% higher breast cancer risk in black women (HR 1.45; 95% CI: 1.10 - 1.90), and 7% higher risk in white women (HR 1.07; 95% CI: 0.99 - 1.16). A higher breast cancer risk was also observed in light-colored dye (HR 1.12; 95% CI:1.02 - 1.23) and dark-colored dye (HR 1.08; 95% CI: 0.98 - 1.19). In contrast, semi-permanent dye and temporary dye use was not associated with risk. This hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. While the findings of present study suggested higher breast cancer risk is associated with personal use of permanent dye, especially among black women, limitations of the study design and analysis need to be considered before jumping to a general conclusion: i) women were recruited to the study because they had a sister with breast cancer (i.e., all subjects in the current study had a significant risk factor of breast cancer), so the conclusions cannot be extended to the wider population; ii) since older age is a strong risk factor for breast cancer, other researcher argued the findings of this study have not been adjusted for age;[43] and iii) confounding factors warrant further examination when adverse effects of endocrine disrupting chemicals (EDC) are to be investigated because exposure to EDC is largely related to environmental and nutritional factors. Social or cultural factors may also associate with patterns in both hair dye usage and breast cancer risk, especially between black and white women.[44] Based on the same cohort, the association between adolescent use of hair dye (subjects at ages of 10 to 13 years, n = 47,522) and breast cancer risk were further investigated.[45] Over 10 years follow-up, 3,380 incident breast cancer cases were diagnosed. Adolescent use of either permanent or semi-permanent hair dye was uncommon (< 3%), and hair coloring products were not associated with breast cancer risk overall (HR 0.97; 95% CI: 0.78 - 1.20) or by menopausal status.

Genetic Polymorphisms

NAT1, NAT2, GSTM1, GSTT1, and Arg72Pro Genotype/Phenotype

Altered genotype and phenotype of liver enzymes may activate or inactivate potential carcinogens.[11] NAT1 and NAT2 genes encode arylamine *N*-acetyltransferases that can deactivate (or, less commonly, potentially activate) arylamine and hydrazine chemicals. Polymorphisms in these genes determine, in part, the liver-function phenotypes. Human populations segregate into rapid, intermediate, and slow acetylator phenotypes. *N*-acetylation is a major route of biotransformation of aromatic amine compounds, including those found in hair dyes. The GSTM1 gene encodes a cytoplasmic glutathione *S*-transferase that belongs to the μ class, which functions in the detoxification of electrophilic compounds (including carcinogens, therapeutic drugs, environmental toxicants, and products of oxidative stress) through conjugation with glutathione. The GSTT1 gene encodes the glutathione *S*-transferase that belongs to the θ class, which catalyzes the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds. Genetic polymorphisms in GSTM1 and GSTT1 also may affect the metabolism of the constituents of hair dyes.

In one study, the association between hair dye use and effect modification by NAT1, NAT2, GSTM1, and GSTT1 genotypes was evaluated among patients with bladder cancer.[11] The hair dye models were adjusted for age, race, sex, and smoking status. An increased risk of bladder cancer was reported primarily among exclusive users of permanent dyes who had NAT2 slow-acetylation phenotypes, compared to never users of dye with NAT2 rapid/intermediate-acetylation phenotypes. This increase was observed in females with a college degree, but the difference was not statistically significant. The authors concluded that NAT1, GSTM1, and GSTT1 genotypes did not appear to be important modifiers of the association between ever, permanent, or exclusive permanent hair dye use and bladder cancer.

One study reported that individuals with the NAT2 slow-acetylator phenotype who exclusively used permanent hair dyes had an increased risk of bladder cancer (OR 2.90; 95% CI: 1.30 - 7.50) after adjustment for cigarette smoking, compared to individuals with the NAT2 rapid-acetylator phenotypes (OR 1.30; 95% CI: 0.60 - 2.80).[46] The NAT*10 allele

contains an altered polyadenylation signal that has been associated with elevated DNA adduct levels and greater risk of bladder cancer in other studies. Individuals with a NAT1*10 genotype who were non-smokers and used permanent hair dyes exclusively had an OR of 1.00 (95% CI: 0.20 - 4.30), and those with a non-NAT1*10 genotype had an OR of 6.80 (95% CI: 1.70 - 27.40) in this study.

A case-control study that evaluated the association of hair dye use with bladder cancer among females also examined the effect of hair-dye use among genetic subgroups.[47] ORs were estimated after adjustment for age, region, and smoking. No statistically significant differences in bladder cancer incidence were noted as a function of any of the genotypes examined, including those with slow- or intermediate/rapid-NAT2 acetylator phenotypes. For NAT2 slow-acetylator phenotypes, the OR was 0.60 (95% CI: 0.30 - 1.40), and for NAT2 rapid/intermediate phenotypes, the OR was 0.90 (95% CI: 0.30 -2.60). Individuals with a NAT1*10 genotype had an OR of 2.90 (95% CI: 0.70 - 11.60), and those with non-NAT1*10 had an OR of 0.60 (95% CI: 0.20 - 1.60). These findings were directionally opposite to those of Gago-Dominguez et al. (2003).[46]

A population-based case-control study was conducted to explore the relationship between hair dye use and the incidence of NHL.[48] The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. Subjects were identified among residents of 4 Surveillance Epidemiology and End Results (SEER) registries (Iowa, Los Angeles County, and metropolitan Detroit and Seattle). There were 101 cases and 98 control subjects reporting no use of hair coloring products and 509 cases and 413 control subjects among the women reporting use of such products, in the population studied. There were 317 cases and 269 control subjects reporting the use of hair dyes before 1980 and 192 cases and 148 controls reporting hair dye use in 1980 or thereafter. The risk estimates were adjusted for age, sex, race and SEER area; education, smoking status, history of farming, having a first-degree relative with a history of NHL or lymphoproliferative malignancy were excluded from the final models because these factors did not materially alter (> 10%) the parameter estimates.

Among the women who started using permanent, intense-tone hair dyes before 1980, those with the NAT2 slow-acetylator phenotype (23 cases/14 controls) or who had no copies of the NAT1*10 allele (26 cases/16 controls) did not have an increased risk of NHL (OR 1.50; 95% CI: 0.60 - 3.60 and OR 1.50; 95% CI: 0.70 - 3.30, respectively). Likewise, women in this subpopulation with 1 or 2 copies of the NAT1*10 allele (22 cases/10 controls) did not have an increased NHL risk (OR 2.50; 95% CI: 0.90 - 7.60, respectively). However, women with the NAT2 rapid/intermediate-acetylator phenotype who started using such dyes before 1980 (25 cases/11 controls) did exhibit a potentially increased NHL risk (OR 3.30; 95% CI: 1.30 - 8.60). There was no evidence of increased risk among women who began using hair dyes after 1980.

One study re-evaluated data from a case-control study of NHL in Connecticut to consider NAT1 and NAT2 genotype/phenotype and 17 other single nucleotide polymorphisms (SNPs).[49,50] The subjects, including 461 cases and 535 control subjects, were identified from the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource (RCASR). Potentially confounding variables included in the final model were age and race. Adjustment for cigarette smoking, alcohol consumption, and farming history were not included in the final models because these factors did not materially alter the parameter estimates. The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale.

With the exception of FL, none of the different individual genes examined was associated with a statistically-significant change in the risk of NHL for any of the NHL subtypes considered. The exception was a statistically-significant increase in the risk of FL in women with rapid/intermediate NAT2 phenotypes who started to use hair dye before 1980, compared with women who never used hair dye (OR 2.80; 95% CI: 1.10 - 7.20; 24 rapid/intermediate acetylator cases vs. 79 control subjects). In women who carried the CYP2C9 allele (TT or CT genotypes) and started to use hair dyes before 1980, there was an increased risk of NHL in general (OR 2.90; 95% CI: 1.40 - 6.10; 58 cases, 43 control subjects) and the follicular lymphoma subtype specifically (OR 6.30; 95% CI: 1.60 - 24.70; 20 cases, 43 control subjects), compared with women who never used hair dyes and women who started using hair dyes in 1980 or thereafter. No association evident in women who carried the CYP2C9 allele (TT or CT genotypes) and started using hair dyes in 1980 or thereafter (23 cases, 46 control subjects), compared with women who carried this allele and never used hair dyes (OR 1.00; 95% CI: 0.40 - 2.30; 23 cases, 46 control subjects).

In a cohort of 327 women (age > 17 years) diagnosed with benign breast disease in Brazil, the SNP Arg72Pro frequency of TP53 gene was investigated.[51] Arg/Pro genotype was the most frequent in the studied population (44.6%), followed by Arg/Arg genotype (39.1%), and Pro/Pro genotype (16.3%). Exposure to hair dyes, straighteners or relaxers were statistically more frequent among women with Arg/Arg genotype (96.1%) when compared with women with another genotypes (p = 0.039). Analysis with Pro/Pro genotype as the reference showed that a strong interaction was observed between exposure to hair products and Arg/Arg genotype (OR 3.26; 95% CI: 1.21 - 8.82).

DNA Repair-Enzyme Genes

One study investigated the interaction between polymorphisms in DNA repair genes and hair dye use with NHL in a population-based case-control study in Connecticut.[52] The study population from which the subjects were drawn was the same as that of Zhang et al. (2009) study[50] summarized above, including 461 cases and 535 control subjects identified from the Yale Comprehensive Cancer Center's RCASR. The subjects included 518 NHL cases and 597 age-matched controls. All subjects were genotyped for 24 single nucleotide polymorphisms (SNPs) in 16 DNA repair-enzyme gene polymorphisms. The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. All of the models were adjusted for age, race, and smoking status. The risk of FL, but not DLBCL, was statistically-significantly elevated in women with any one of 10 of the 24 SNPs and who used hair dye before 1980, compared to those who never used hair dyes; the ORs ranged from 1.93 (95% CI: 1.00 - 3.72; 15 cases and 70 control subjects with EECC1rs3212961 CC) to 3.28 (95% CI: 1.27 - 8.50; 7 cases and 110 control subjects with BRCA2rs144848 AC+CC). In addition, there was a statistically-significant interaction between hair dye use before 1980 and NHL in women with one of these 10 SNPs (OR 1.88; 95% CI: 1.26 - 2.80; 146 cases and 100 control subjects with WRNrs1346044 TT). There was no association between NHL, FL, or DLBCL in women who began using hair dyes after 1980.

PREVIOUS CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

Table 1. Hair Dye Epidemiology Studies considered by the Panel.

Study Type/Methodology	Results	Reference
Bladder Cancer		
Population-based case-control study in the Netherlands. Cases diagnosed between 1975 and 2009 for a total of 246 female cases with 2587 female controls; Analyses were not performed for the men selected for the study because less than 5% reported ever using hair dyes.	No association between bladder cancer and ever/never use of permanent hair dyes – permanent OR = 0.87 (95% CI: 0.65-1.18); temporary OR = 0.7 (95% CI: 0.58-1.02) No association between bladder cancer and duration of use, number of times used per year, total number of times used over a lifetime, dying all the hair or only part of the hair, or dye color (none of the subjects reported use of black dye). No association found when patients stratified by aggressiveness of the cancer.	Ros et al (2012)[10]
Population-based case-control study in Maine, Vermont, and New Hampshire. Cases diagnosed 2001 to 2004 for a total of 1193 cases (911 male and 282 female) with 1418 controls (1039 male and 378 female). Genotyping done for NAT2, NAT1, GSTM1, and GSTT1.	No association between ever/never use of hair dyes and bladder cancer – women OR = 0.7 (95% CI: 0.5-1.0); men OR = 0.7 (95% CI: 0.4-1.0). No association between hair dye use, NAT2 phenotype or NAT1 genotype and bladder cancer risk. Increased risk of bladder cancer with permanent hair dye use in a subgroup of women with a college degree, but no dose-response for color, duration of use, or total lifetime uses. NAT2 phenotype was associated with a suggestive, but not statistically significant, increased risk when college-degreed women were stratified by education – this was based on 15 cases and 6 controls.	Koutros, et al. (2011)[11]
Population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls (identified using the Iranian cancer registry).	Overall (male and female) OR for hair dye use and bladder cancer was 1.99 (95% CI: 1.02-3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was reported.	Shakhssalim et al. (2010)[12]

Prostate Cancer		
Hospital-based case-control study of prostate cancer in Taiwan with 296 cases and 296 controls Another 608 incident prostate cancer cases were investigated to determine the rate of prostate cancer survival.	The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (adjusted OR 2.15; 95% CI: 1.32-3.57). Personal hair dye use increased risk of prostate cancer with a dose-response effect. Of the 608 cases, 26.4% (161/608) reported having used hair dyes. The use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths ($p = 0.753$).	Tai et al. (2016)[13]
Lymphoma and Leukemia		
Cohort or case-control study of leukemia in North America, Europe and Asia.	Multivariate analysis: Based on 20 studies, ever use of any type of personal hair dye was associated with a non-statistically significant increased risk of leukemia, when compared to no use of hair dye (meta-RR 1.09; 95% CI: 0.97-1.22). A model restricted to case-control studies yielded a statistically significant increased RR of 1.13 (95% CI: 1.00-1.28), while a model including cohort studies yielded an RR of 1.00 (95% CI: 0.85-1.19). When restricted to studies that adjusted for smoking history, use of any hair dye was not associated with leukemia (RR 0.99; 95% CI: 0.76-1.29).	Towle et al. (2017)[16]
Population-based case-control study of leukemia and non-Hodgkin's lymphoma (NHL) in Italy. There were 161 cases (120 lymphoid and 41 myeloid) and 84 randomly-selected controls among women in the population studied.	Multivariate analysis: Hair dye use for at least 15 years was associated with NHL (OR 2.3; 95% CI: 1.00-4.90), but hair dye use for less than 15 years was not associated with NHL (OR 1.40; 95% CI: 0.60-3.10). Leukemia was not associated with using hair dye for at least 15 years (OR 2.70; CI 0.90-7.90) or for less than 15 years (OR 2.70; CI 0.90-8.40).	Parodi et al. (2016)[17]
Hospital-based case-control study of lymphoproliferative cancers in Egypt. There were 130 cases (107 NHL and 23 chronic lymphocytic leukemia) and 130 age- and sex-matched controls.	Multivariate analysis: No increase in the risk of lymphoproliferative disorders with history of using hair dyes (χ^2, $p > 0.05$).	Salem et al. (2014)[21]
Hospital-based case-control study of myelodysplastic syndromes (MDS) in China. There were 403 cases and 806 controls.	Univariate analysis: OR for hair dye use (≥ 2 times per year) and all MDS was 1.46 (95% CI: 1.03-2.07). Multivariate analysis: OR was 1.31 (95% CI: 0.88-1.93).	Lv et al. (2010)[22]
Hospital-based case-control study in Shanghai of NHL. There were 649 cases and 1,[23]298 controls	No increased risk of NHL, with an OR of 0.93 (95% CI: 0.75-1.16). For chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use with an OR of 0.37 (95% CI: 0.18-0.76).	Wong et al. (2010)[23]
Re-evaluated tissue samples from an NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence in situ hybridization) cytogenetic technique to evaluate both *t*-positive and *t*-negative NHL subtypes.	An association between ever/never use of hair dyes and t(14;18)-negative NHL (OR 2.90; 95% CI: 1.60-5.00) and bcl-2 positive NHL (OR 2.20; 95% CI: 1.40-3.40), but not with t(14;18)-positive NHL (OR 1.30; 95% CI: 0.60-2.60) or bcl-2 negative NHL (OR 1.40; 95% CI: 0.50-3.80).	Chang et al. (2010)[24]
Hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1,444 controls.	No increase in the risk of AML with personal use of hair dyes; OR = 0.98 (95% CI: 0.80-1.20).	Wong et al. (2009)[25]
Hospital-based case-control study of ALL in Iran with 125 cases (age younger than 15) and 130 controls.	No association was found between mother's use of hair dye during pregnancy and the risk of ALL (OR 0.87, 95% CI: 0.32-2.37).	Rafieemehr et al. (2019)[26]
Hospital-based case-control study of leukemia in Pakistan with 25 adult leukemia cases and 50 gender- and marital status-matched controls,	Increased leukemia risk was observed among hair dye users. The un-adjusted OR was 4.14 (95% CI: 1.28-4.95) for adults and 4.60 (95% CI: 1.57-4.60) for children, respectively. Other leukemia	Arshad et al. (2018)[27]

and 40 children cases and 80 age- and gender-matched controls.	risk factors for adult subjects included exposure to chemical factory ($p < 0.05$), a positive family history of leukemia ($p < 0.006$), a positive trauma history ($p < 0.004$) and born 1st or 4th among their siblings ($p < 0.037$). Children at a greater risk of leukemia also had a positive trauma history ($p < 0.000003$), a positive family history of leukemia ($p < 0.0484$), and live-in radiation area ($p < 0.00007$).	
Hospital-based case-control study of childhood leukemia in China with 958 cases (580 boys, 378 girls) and 785 controls (449 boys, 336 girls).	In multivariable logistic regression analysis, smoking during pregnancy (OR: 3.55; 95% CI: 1.05-12.41), a history of using birth control pills before pregnancy (OR: 1.795, 95% CI: 1.08-2.98), and parents use of hair dye during breastfeeding (OR 13.56; 95% CI: 1.11-165.21) were associated with increased risk of childhood leukemia. A family history of malignant tumors (OR: 4.14; 95% CI: 2.52-6.81), a family history of neoplasm of the lymphatic/hematopoietic systems (OR: 7.65; 95% CI: 2.33-25.06), and Down's syndrome (OR: 8.60; 95% CI: 2.02-36.58) were also identified as significant risk factors for childhood leukemia. Ever breastfed was significantly different from never breastfed (OR: 7.43, 95% CI: 5.12-10.78), suggesting a protective effect of breastfeeding against childhood leukemia.	Gao et al. (2018)[28]
Testicular Cancer		
Case-control study of TGCT in the US with 527 mothers of TGCT cases and 562 mothers of controls.	Maternal use of hair dye (OR 0.80; 95% CI: 0.54-1.18), hairspray (OR 1.17; 95% CI: 0.89-1.55), or permanent wave (OR 1.18; 95% CI: 0.86-1.62) during pregnancy and breastfeeding was not associated with TGCT risk in sons.	Ghazarian et al. (2018)[32]
Breast Cancer		
Population-based case-control study of breast cancer in African American and European American women in New York city and 10 counties in New Jersey. There were 1508 African American and 772 European American cases and 1290 African American and 715 European American frequency-matched (by age and county of residence) control subjects.	Increase in the odds of breast cancer in African American women who reported using dark permanent hair dyes (OR 1.52; 95% CI: 1.21-1.91), African American women who typically had their hair dyed in a salon (OR 1.30; 95% CI: 1.03-1.63), and European American women who had a history of both hair dyes and chemical hair relaxers (OR 2.21; 95% CI: 1.26-3.86). Women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter.	Llanos et al. (2017)[34]
Population-based case-control study of breast cancer in Finland. There were 6,567 cases and 21,598 age-matched controls.	Increase in the odds of breast cancer in women who ever used hair dyes, compared with those who never used hair dyes (OR 1.28; 95% CI: 1.10-1.48). Statistically significant trend in ORs for cumulative use of hair dyes (1.07 and 1.31 for 1-2 episodes and 35-89 episodes, respectively). In comparison, the OR decreased from 1.28 (10 - 34 dye episodes) and 1.31 (35 - 89 dye episodes) to 1.25 ($\geq$ 90 dye episodes).	Heikkinen et al. (2015)[35]
Prospective population-based cohort study of breast cancer in China. Cases of breast cancer include 234 hair dye users and 358 non-users.	No increase in the relative risk of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR 0.93; 95% CI: 0.78-1.09). Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women.	Mendelsohn et al. (2009)[36]
Hospital based case-control study in the UK. There were 191 cases and 561 age matched controls. 73 cases and 213 controls had ever used hair dyes.	A non-statistically significant increase in the relative risk of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR = 1.01). There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.	Kinlen et al. (1977)[37]
Hospital based case-control study in Canada and London. There were 85 cases and 170 controls, both over two locations.	A non-statistically significant increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (London: RR = 1.30; 95% CI: 0.60-2.50 and Toronto, Ontario: RR = 1.10; 95% CI: 0.50-2.40). Further statistical analyses, allowing for smoking habits, family history of cancer	Stavraky et al. (1979)[38]

	and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.	
Hospital based case-control study in New York City with 398 cases and 90 randomly selected, age-matched controls.	No increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (OR 0.80; 95% CI: 0.60-1.10). There was also no statistically significant difference between those who report using hair dyes at least once and those who reported more than 100 uses.	Koenig et al. (1991)[39]
Hospital-based case-control study in Iran with 526 newly diagnosed breast cancer cases and 526 randomly selected, age-matched controls.	Multiple factors contribute to the risk of breast cancer, such as hair coloring, stress, and smoking. The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI: 1.41-2.62).	Dianatinasab et al. (2017)[40]
Prospective cohort study of breast cancer in the United States and Puerto Rico. Sister Study subjects included 46,709 women aged 35-74 enrolling from 2003 to 2009, who had no history of breast cancer but had 1 or more sisters with breast cancer.	There was no association between semi-permanent dye/temporary dye use and breast cancer risk. The hazard ratio for breast cancer was 1.45 (HR 1.45; 95% CI: 1.10-1.90) and 1.07 (HR 1.07; 95% CI: 0.99-1.16) for permanent dye use in black women and white women, respectively. A higher breast cancer risk was also observed in light-colored dye (HR 1.12; 95% CI:1.02-1.23) and dark-colored dye (HR 1.08; 95% CI: 0.98-1.19). Personal straightener use was associated with 18% higher breast cancer risk (HR 1.18; 95% CI: 0.99-1.41), and more frequent straightener use was associated with higher risk (p for trend = 0.02). Nonprofessional application of semipermanent dye to others was associated with breast cancer risk. (HR 1.28; 95% CI: 1.05-1.56).	Eberle et al. (2020)[42]
Prospective cohort study of breast cancer in the United States and Puerto Rico. Sister Study participants (n=47,522) who had completed enrollment questionnaires between 2003 and 2009 on hair dyes use at ages 10 to 13 years.	Hair dyes use were not associated with breast cancer risk overall or by menopausal status: permanent or semi-permanent hair dye use during adolescence was uncommon (< 3%) and not associated with breast cancer overall (HR 0.97, 95% CI: 0.78-1.20 and HR 0.87, 95% CI:0.68, 1.12, respectively). A higher risk for breast cancer was observed in black women (HR 1.77, 95% CI: 1.01-3.11; n = 13), but among white women (HR 0.93, 95% CI: 0.74-1.18; n = 70).	White et al. (2020)[45]

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Memorandum

Date: February 16th, 2021

From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review

To: All Stakeholders

Re: 2022 Draft Priority List

The CIR Procedures require preparation of the 2022 Draft Priority List for public comment by June 1, 2021. However, it is advantageous for the 2022 Draft Priority List to be issued for public comment earlier (March 2021) in the process to allow more time for the acquisition of data. The priority list is typically based on stakeholder requests (e.g., a hair dye) and frequency of use (FOU) data from FDA's Voluntary Cosmetic Registration Program (VCRP); this year, VCRP data were received from the FDA on January 21 (in response to a Freedom of Information Act request).

While this list includes only the lead ingredients, groupings of ingredients, drafted by CIR Staff, can be found on the following pages. However, for those ingredients which comprise discrete organic chemicals, the Panel Grouping/Clustering Working Group will provide their consideration.

There are 7 reports proposed (2 of the lead ingredients below are proposed to be reviewed together in 1 report) on the 2022 Draft Priorities List. Once a proposal of a hair dye for assessment has been received from the PCPC Hair Color Technical Committee, 8 new reports in total will be proposed for the 2022 docket. Reports previously prioritized and on the CIR docket at the end of 2021, as well as an extensive number of re-reviews of previous assessments, will supplement the total number of reports to be assessed in 2022.

Interested parties are encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews for these ingredients. Although the specific data needs vary for each safety assessment, the following are typical data that the Panel reviews for each safety assessment.

- Chemistry, impurities, and method of manufacture
- Toxicokinetics data, specifically dermal absorption and/or penetration
- Repeated-dose toxicity data
- Inhalation toxicity data, if the ingredient is used in a product that can be incidentally inhaled

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- Reproductive/developmental toxicity data
- Genotoxicity data; if positive, carcinogenicity data may be needed
- Dermal irritation and sensitization data at maximum concentration of use

For the review of botanical ingredients, the additional data needed include: species, plant part, extraction method, solvent, and data on component chemical characterization. It is important that these data are specific for the ingredient(s) as used in cosmetics.

2022 Draft Priorities List

Ingredients	Frequency of Use (FOU) Data Year 2021
For cause	
To be determined **– a hair dye**	-
Per FOU	
Sodium Acetylated Hyaluronate	**305**
Hydrolyzed Hyaluronic Acid	**269**
Polyhydroxystearic Acid	**264**
Diphenylsiloxy Phenyl Trimethicone	**251**
Trisodium Ethylenediamine Disuccinate	**236**
Charcoal Powder	**229**
Zanthoxylum Piperitum Fruit Extract	**217**
Pyridoxine HCl	**197**

2022 Draft Priorities Groupings for New Reports

Proposed 2022 Report – per cause

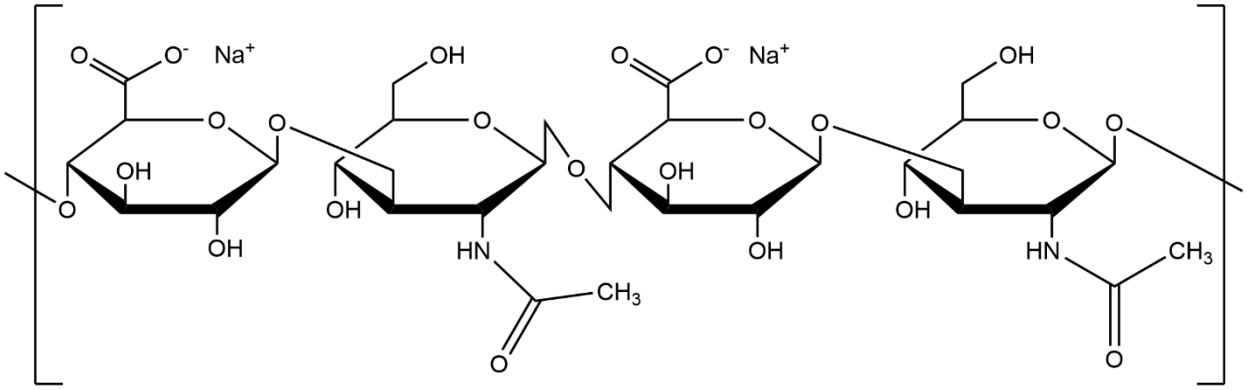
To be determined *– per PCPC Hair Color Technical Committee(HCTC)* **FOU = __**

Reported **Function**: Hair Colorant
Notes: *Since FOU might not be a very accurate surrogate for exposure, with regard to hair dyes, the PCPC HCTC proposes one hair dye ingredient annually for CIR review. The HCTC typically submits a proposed hair dye ingredient between the 1st and 2nd meetings of the year.*
Grouping proposal: None

Proposed 2021 Reports – per FOU

Sodium Acetylated Hyaluronate **FOU = 305**
& Hydrolyzed Hyaluronic Acid **FOU = 269**

Definition: Sodium Acetylated Hyaluronate is the acetyl ester of Sodium Hyaluronate. Hyaluronic Acid is the natural mucopolysaccharide formed by bonding *N*-acetyl-D-glucosamine with glucuronic acid.



Hyaluronic Acid

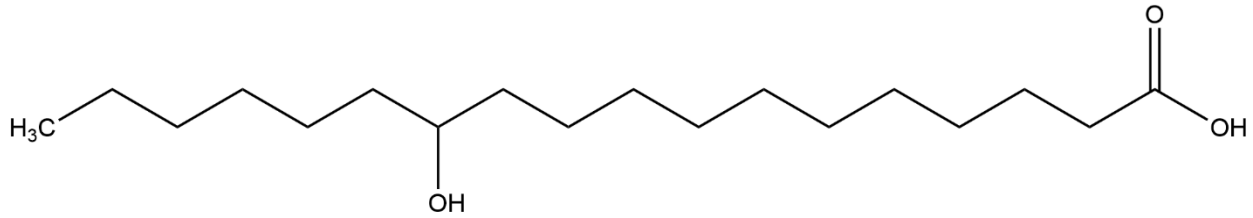
Reported **Functions**: Humectants; Hair Conditioning Agents; Viscosity Increasing Agents;
Notes: *(No CAS Nos.)* Published in 2009, the Panel concluded "that Hyaluronic Acid, Sodium Hyaluronate, and Potassium Hyaluronate are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment."
CIR draft grouping/clustering: (6 ingredients proposed with a total FOU = 4942)

Subject to approval by Grouping/Clustering Working Group	***FOU***
Sodium Acetylated Hyaluronate	*305*
Hydrolyzed Hyaluronic Acid	*269*
Hyaluronic Acid	*529*
Sodium Hyaluronate	*3757*
Potassium Hyaluronate	*23*
Hydrolyzed Sodium Hyaluronate	*59*

Polyhydroxystearic Acid

FOU = 264

Definition: Polyhydroxystearic Acid is a polymer of Hydroxystearic Acid. Hydroxystearic Acid is the fatty acid that conforms generally to the formula:



Reported **Functions**: Surfactants

Notes: *(CAS Nos. 27924-99-8 & 58128-22-6)* Published in 2019, the Panel concluded that hydroxystearic acid and other fatty acids are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a QRA.

CIR draft grouping/clustering: *(3* ***ingredients proposed with a total FOU = 290)***

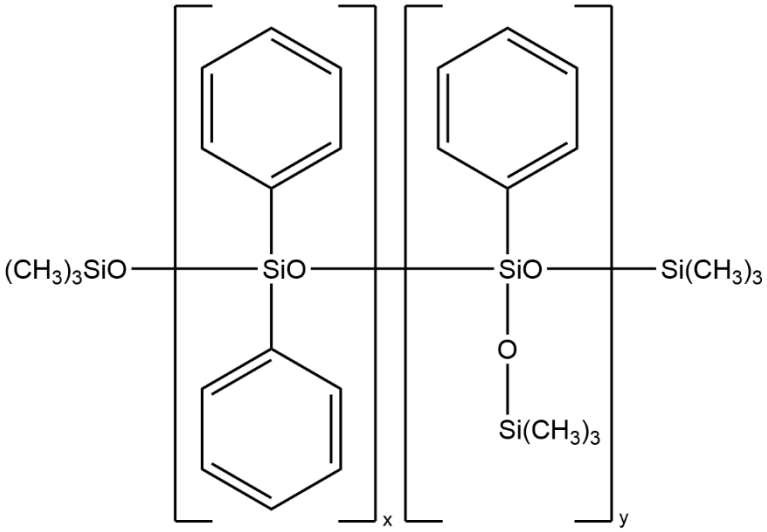
Subject to approval by Grouping/Clustering Working Group

Polyhydroxystearic Acid	*264*
Poly(3-Hydroxyoctanoic Acid)	*-*
Polylactic Acid	*26*

Diphenylsiloxy Phenyl Trimethicone

FOU = 251

Definition: Diphenylsiloxy Phenyl Trimethicone is the silicone compound that conforms to the formula:



Reported **Functions**: Antifoaming Agents; Hair Conditioning Agents;

Notes: *(CAS No. 352230-22-9) Published in 2014, the Panel concluded that Dimethicone/Phenyl Vinyl Dimethicone Crosspolymer, Diphenyl Dimethicone Crosspolymer, and other "dimethicone crosspolymer ingredients are safe in the practices of use and concentration as given in this safety assessment." Published in 2017, the Panel concluded that Dimethiconol/Stearyl Methicone/Phenyl Trimethicone Copolymer and other dimethiconal copolymer "ingredients are safe in the present practices of use and concentration described in this safety assessment." Published in 1986 (and not reopened in 2006), the Panel concluded that "Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration."*

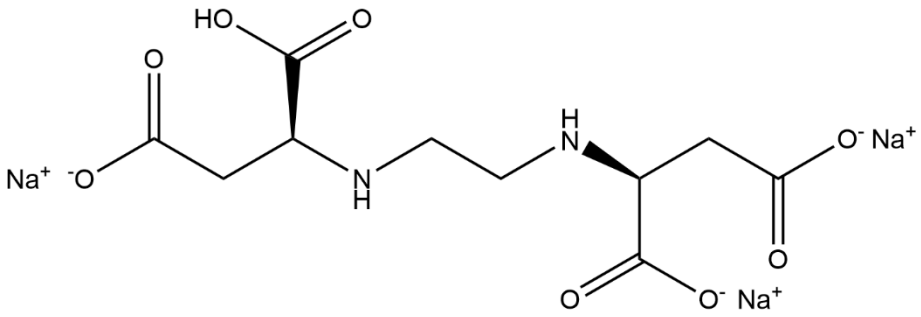
CIR draft grouping/clustering: (9 ingredients proposed with a total FOU = 1283)

Subject to approval by Grouping/Clustering Working Group	**FOU**
Diphenylsiloxy Phenyl Trimethicone	*251*
Diphenyl Dimethicone	*113*
Diphenylsiloxy Phenyl/Propyl Trimethicone	-
Hydrogen Diphenyl Dimethicone	-
Phenyl Dimethicone	-
Phenyl Methicone	*2*
Phenyl Trimethicone	*850*
Trimethylsiloxyphenyl Dimethicone	*67*
Triphenyl Trimethicone	-

Trisodium Ethylenediamine Disuccinate

FOU = 236

Definition: Trisodium Ethylenediamine Disuccinate is the organic compound that conforms to the formula:



Reported **Functions**: Chelating Agents

Notes: *(CAS Nos. 178949-82-1 & 474787-13-8)*

CIR draft grouping/clustering: (2 ingredients proposed with a total FOU = 245)

Subject to approval by Grouping/Clustering Working Group	***FOU***
Trisodium Ethylenediamine Disuccinate	*236*
Tetrasodium Iminodisuccinate	*9*

Charcoal Powder

FOU = 229

Definition: Charcoal Powder is finely ground, Charcoal. Charcoal is the dried, carbonaceous material obtained from the heating of organic substances.

Reported **Functions**: Abrasives; Absorbents; Colorants; Opacifying Agents

Notes: *(CAS Nos. 7440-44-0 & 16291-96-6)*

CIR draft grouping/clustering: (4 ingredients proposed with a total FOU = 282)

	FOU
Charcoal Powder	*229*
Charcoal	*-*
Charcoal Extract	*8*
Activated Charcoal (not an INCI name, but listed in VCRP)	*45*

Zanthoxylum Piperitum Fruit Extract

FOU = 217

Definition: Zanthoxylum Piperitum Fruit Extract is the extract of the fruit of *Zanthoxylum piperitum*. *Zanthoxylum piperitum* is commonly called Sichuan pepper.

***Reported* Functions**: Skin-Conditioning Agents - Miscellaneous

Notes: *(CAS No. 97404-53-0)*

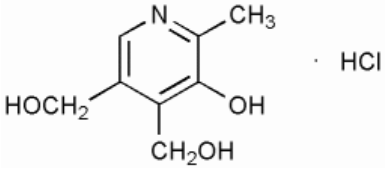
CIR draft grouping/clustering: (4 ingredients proposed with a total FOU = 234)

	FOU
Zanthoxylum Piperitum Fruit Extract	*217*
Zanthoxylum Piperitum Oil	*-*
Zanthoxylum Piperitum Peel Extract	*17*
Zanthoxylum Piperitum Peel Water	*-*

Pyridoxine HCl

FOU = 197

Definition: Pyridoxine HCl is the substituted aromatic compound that conforms to the formula:



***Reported* Functions**: Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous

Notes: *(CAS No. 12001-77-3 & 58-56-0)*

CIR draft grouping/clustering: (2 ingredients proposed with a total FOU = 236)

Subject to approval by Grouping/Clustering Working Group	***FOU***
Pyridoxine HCl	*197*
Pyridoxine	*39*